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(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.

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Description

NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

5 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEQ ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEO ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 15 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

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157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

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Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computerreadable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment 5 that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 10 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag[™] peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide, thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

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"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

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The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

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"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α -globin, β -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

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The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

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A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436. Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, *Nuc. Acids Res.* 14:4683, 1986) are not always exact and may vary by as much as ± 5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

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Table 1

<u>Protein</u>	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	. 82	21
AFP310695	84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15

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AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	20 17
AFP356885	130	17
AFP226938	130	
		16
AFP138504	134	29
AFP359196	136	24
AFP501809	138	27
AFP152733	140	15
AFP541394	142	23
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15
. I. I J V U J J	100	13

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	· 23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270 ·	16
AFP275580	270 272	28
AFP273380 AFP298054		28 21
AFP348226	274 276	21 23
· ·	276	23
AFP349106	278	
AFP288248	280	15
AFP436476	282	19

AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP323713		20
AFP327160 AFP329002	360	
	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	25

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AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	. 19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27

A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein 5 disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the 10 present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

15.

AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and antiviral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., *J. Biol. Chem.* 227:5784-5789, 1996). This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

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Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

5 Table 3

	1 able 3
Locus	Accession Number & Description
AFP130852	AE003823 (fly genomic)
AFP169968	AE003515 (fly genomic)
AFP174843	AF283518 (Mus musculus elongation factor sec)
AFP176427	AE003808 (fly genomic)
AFP178828	PSN_V61483
AFP179530	AE003708 (fly genomic)
AFP188135	AE003677 (fly genomic)
AFP195042	PIR_T41241 (yeast oxysterol-binding protein family)
AFP198645	AE003718 (fly genomic)
AFP199200	AF113691 (human clone FLB4739 PRO1238 mRNA)
AFP204736	AC069237 (human chromosome 3 clone RP11-175M9)
AFP229269	AF247177 (Mus musculus sphingosine-1-phosphate
	phosphohydrolase)
AFP230872	AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AFP279267	AE003559 (fly genomic)
AFP347179	AE003499 (fly genomic) Z1041035F6P
AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP359196	AE003530 (fly genomic)
AFP374312	AE003538 (fly genomic)
AFP389687	AE003831 (fly genomic)
AFP395942	AB041564 (mouse brain cDNA; clone MNCb-0914)
AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP477303	AE003778 (fly genomic)
AFP62060	PSP_Y94938 (Human secreted protein clone ye78_1)
AFP71288	AL161655 (human chromosome 20 clone RP11-116E13)
AFP74517	PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone:RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

Locus	Accession Number & Description
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology
	to PSP_W35393 Human TB2 gene product)
AFP202885	AB037808 (human mRNA for KIAA1387 protein)
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)
AFP250422	AF208849 (human BM-007 mRNA)
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to
	major facilitator protein homolog, fission yeast: PIR_S62432)
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak
	homology to dinitrogenase reductase activating glycohydrolase (draG)
	Archaeoglobus fulgidus: PIR_C69465)
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on
	chromosome 10. Contains a novel gene and the 5' end of the gene for a
	novel protein; ortholog of mouse FISH protein) .
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:
	Human O-linked GlcNAc transferase mRNA)

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker 5 peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically 10 engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to $E.\ coli\ \beta$ -galactosidase (1,021 residues; see Casadaban et al., $J.\ Bacteriol.\ 143:971-980,\ 1980)$, a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

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Nucleotide Resolutions Complement Resolutions Α Α T T C C G G G G C \mathbf{C} T T Α Α Y CT R AG Y C|TA|GR G|TM A|CK K G|TAC M S CIG S C|G W A|TAIT W H A|C|T D A|G|T CIGIT V A|C|G В V A|C|G CGT В D AIGIT Η A|C|T N A|C|G|T N A|C|G|T

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter		Degenerate
Acid	Code	Codons	Codon
Cys	С	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	A	GCA GCC GCG GCT	GCN
Gly .	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	Н	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTC TTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	•	TAA TAG TGA	TRR
Asn Asp	В		RAY
Glu Gln	Z	*	SAR
Any	X		NNN
Gap	-		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

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exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

5

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

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Table 8

K562 cells
T-cells
testis
fetal liver or spleen
fetal liver or spleen
testis
placenta
fetal liver or spleen
adult brain
epidermal breast keratinocytes
breast
infant brain
testis
testis
fetal heart
K562 cells
testis
infant brain
germinal center B-cells
kidney
neonatal keratinocytes
peripheral blood eosinophils of asthma patients
K562 cells
fetal liver or spleen
testis
pregnant uterus
germinal center B-cells
fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex TaqTM; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or AdvantageTM 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

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Table 9	12	y	^	^	^	_>	_	, >	>	>	Λ	У	۳	u	y	y	=	γ	λ	u	γ	y	ک	y	γ	^	y	у	λ	у	λ	y	ء
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	10	y	y	^	^	>	_	^	Ž	y	y	у	u	u	У	y	У	у	y	u	y	у	у	y	Λ	у	у	У	У	y	y	y	L L
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	Protein	AFP11750	AFP127023	AFP137186	AFP138504	AFP138740	AFP177000	AFP178828	AFP179530	AFP188135	AFP194554	AFP195562	AFP198645	AFP199044	AFP199200	AFP229269	AFP236718	AFP237679	AFP244615	AFP249599	AFP250422	AFP262739	AFP266188	2755	AFP27745	AFP279267	AFP280451	AFP290397	AFP293220	AFP297548	AFP30659	AFP313600	AFP324422
	Pa	AF	AF	ΑF	ΑF	AF	AFI	AFI	AFI	AF	AFI	AFI	AFI	AFI	AFI	AFI	AF.	¥.	AFI	AFI	AFI	AF	AFI	YE.	AFI	AFI	A.F.	AFI	AFI	AFI	YE!	F	AFI
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Table 9, continued	nued																•				
Protein	1 2	_	3	4 5	9	1	∞	6	10	11	12	13	14	15	9	11	82	6	22	21	22
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peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H₂O; 22, genomic DNA. Y=yes; n=no; nd=not determined. Tissues screened were: 1, brain; 2, heart; 3, kidney; 4, liver; 5, lung; 6, pancreas; 7, placenta; 8, skeletal muscle; 9, colon; 10, ovary; 11,

Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

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The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable), digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning et al., *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (e.g., Sf9 or Sf21 cells) or *Trichoplusia ni* (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10⁵ cells to a density of 1-2 x 10⁶ cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, *ibid.*; O'Reilly et al., *ibid.*; Richardson, *ibid.*). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides 5 therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. 15 Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (Bangalore) 11:47-58, 1987.

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Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

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Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

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Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, Chem. Pept. Prot. 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the CytosensorTM Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

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Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., *Investigational New Drugs* 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, *Methods Enzymol.* 109:749-773, 1985; Wahl et al., *Mol. Cell Biol.* 8:5016-5025, 1988; and Cook et al., *Analytical Biochem.* 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., *J. Immunol. Methods* 82:169-179, 1985), and use of tetrazolium salts (Mosmann, *J. Immunol. Methods* 65:55-63, 1983; Alley et al., *Cancer Res.* 48:589-601, 1988; Marshall et al., *Growth Reg.* 5:69-84, 1995; and Scudiero et al., *Cancer Res.* 48:4827-

4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

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In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO₂ atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. ³H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, J. Immunol. Methods 120:271-276, 1989; Greenfeder et al., J. Biol. Chem. 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as ³H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, ibid.).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using ³H-proline incorporation into nascent secreted collagen.

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SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1β and TNFα levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

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Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (*J. Biol. Chem.* 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately 10^4 - 10^5 cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, *Science*

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-10 429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. 183:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 α or IL-1 β is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g., γ counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol*: 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol*. 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACoreTM, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

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chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic 5 peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant K_i is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin 15 (Steiner et al., <u>J. Biol. Chem.</u> 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. <u>270</u>:25411-25417, 1995).

Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

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Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

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An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., *J. Biol. Chem.* 263:14621-14624, 1988; Wu et al., *J. Biol. Chem.* 267:963-967, 1992; and Johnston and Tang, *Meth. Cell Biol.* 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition in vivo. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, *Brit. J. Dermatol.*

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118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive 5 days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB₄ levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton 20 et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO₂/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine*

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., *Arch. Surg.* 128:423-429, 1993). A test substance is injected subcutaneously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, Advan. Enzyme Regul. 35:293-301, 1995; Conway et al., Clin. Exp. Metastasis 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, Semin. Thromb. Hemost. 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* <u>81</u>:3998-4002, 1984.

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Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Ta</u>	<u>'able 10</u>							
<u>Protein</u>		<u>Hexa</u>	peptide N	-termini						
AFP210015	389	405	97	388	359					
AFP170681	51	334	113	49	140					
AFP413680	221	207	220	206	198					
AFP483037	219	218	82	216	215					
AFP230872	189	188	73	156	68					
AFP178828	211	210	209	208	207					
AFP200134	150	149	146	132	145					
AFP195796	99	97	111	208	240					

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	· 29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23 -	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885 -	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

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AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	592	591	374	525
AFP75785	128	127	136	[.] 99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71 -	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	1.1.8	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2 .	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

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AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')2 and Fab fragments, single chain antibodies, and the like, including genetically engineered 5 antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire nonhuman variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K_a) of 10⁶ M⁻¹ or greater, preferably 10⁷ M⁻¹ or greater, more preferably 10⁸ M⁻¹ or greater, and most preferably 10⁹ M⁻¹ or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, Ann. NY Acad. Sci. 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity *in vitro* and *in vivo*.

The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, Pseudomonas exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., ibid., ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, the **OMIMTM** Database, Johns Hopkins University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

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Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

			Ta	Table 11			
AFP	GenBank Acc. No.	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
AFP127023	AP001155	RP11-594B10	*	18	18q12	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	11	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	51	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	15		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11-	*	14	14q23.3	62132030	62313415
		116N21;RP11-7F17					
AFP179530	AC011475	CTC-539A10	*	12	12q12	41234876	41456630
AFP188135	AC013740	*	*	6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	16	16q22.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	91	16q11.2	44574019	44904017
AFP.199200	CNS01DV7	BAC-R-1070N10	*	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14q21.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	60L69Z	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055 3	3	3q13.12	116466893	116517043
AFP249599	AL157714	RP11-541H12	*	1	1q22-23.3	161893354	162136704
AFP250422	AC012046	RP11-312P12	*	01	10q22.1	81289799	81650062
AFP262739	AC005884	hRPK.264_B_14	*	<i>L</i> 1	17q23.3	64245127	64365313
AFP275580	AC016773	*	*	3	3q21.3	141329005	141513510
AFP277451	AC055822	RP11-707M3	*	8	8q13.3	75395740	75583383
AFP279267	*	*	AI566086	. 01	10q11.1	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	10	10q24.32	115276306	115467187
AFP290397	*	*	AA421069	15	15q15.3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	*	W52728	11	11911	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP325761	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

20153358	44286594	126134148	138765140	128134589	3500834	4222465	143641730	1514256	59940397	19003942	173547400	70471703	16677574	50564907	60714738	108794286	137478427	*	77633569
19959493	44087441	125918909	138667522	128134250	3479999	4189155	142961410	1512179	59897688	18993217	173540737	70222075	16491516	50554924	60450247	108494503	137477811	*	77419530
14p11.1	17q21.2	12q24.23	1q12-21.2	11q23.3	16p13.3	16p13.3		4p16.3	19q13.33	8p21.3	5q33.1	16q22.1	19p13.13	6p21.1	13q21.1	13q34	6q22.33	1p35.1-36.13	4q21.22
14	17	12	-	=	16	16	1	4	19	∞	5	16	19	9	13	13	9	_	4
AI525611	*	*	*	AI253088	AI741157	*	AI133727	AI341602	*	AI814257 ·	AI140615	*	*	AW583171	*	*	AA493506	*	*
BAC-R-407N17	CTD-2534121	*	3.28E+21	*	*	*	*	*	cosmid-R31181	*	*	RP11-502K10	CTB-5E10	*	RP11-342J4	RP11-391H12	*	RP5-1056L3	RP11-791G16
AL132639	AC015936	AC025740	AL022240	*	*	AC004235	*	*	AC006942	*	*	AC009131	AC008686	*	AL138695	AL136221	*	HS1056L3	AC067942
AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517	AFP93743

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet 15 et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

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(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other 5 binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a 15 ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

The bioactive conjugates described herein can be delivered intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

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For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

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Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDrawTM (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds. x-ray crystallography to determine the three-dimensional structure in atomic detail. nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

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students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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EXAMPLES

Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His₆ tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique SmaI site just downstream of the MBP-His₆-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of SmaI-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura⁺ transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (*ibid.*). 100-ml cultures in minimal glucose media containing casamino acids and 100 μg/ml ampicillin are grown at 37°C in 500-ml baffled flasks to $OD_{600} \approx 0.5$. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at 70°C.

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Example 3

For larger-scale protein preparation, 500-ml cultures of *E. coli* BL21 expressing the AFP-MBP-His₆ fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH₂PO₄, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 μ g/ml Leupeptin, 2 μ g/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with SmaI, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (*S. cerevisiae*) cells are independently combined with 10 μ l of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μ F. To each cuvette is added 600 μ l of 1.2 M sorbitol, and the yeast is plated in two 300- μ l aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H₂O]) and incubated at 30°C. After about 48 hours, the Ura⁺ yeast

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transformants from a single plate are resuspended in 1 ml H₂O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 µl acid-washed glass beads and 200 µl phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 µl ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 µl H₂O.

Transformation of electrocompetent *E. coli* host cells (Electromax DH10BTM cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% BactoTM Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% BactoTM Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO₂, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (LipofectamineTM Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

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mixed with 605 μl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 μM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEO ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:
 - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
 - a transcription terminator.
- The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 12. 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- A cultured cell comprising the expression vector of claim 11 or claim 13. 12.
- A method of producing a polypeptide comprising culturing the cell of 14. claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
 - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

a transcription promoter;

- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

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SEQUENCE LISTING

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	His			165					170		·	•		175	•
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aca Thr									-					cat His		624

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	tgg Trp 290	_	-	-	_	_				-			-		912
	acg Thr				_	_		-					-	_	960
	gca Ala		_			_			-	-		_	_		1008
	ccc Pro						-	-						_	1056
	gat Asp													-	1104
	999 Gly 370	_		_	_							-		_	1152

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180 185 190 Thr Lys Thr Trp Ser Val Met Pro Pro Met Ser Thr His Arg His Gly 200 Leu Gly Val Ala Val Leu Glu Gly Pro Met Tyr Ala Val Gly Gly His 215 220 Asp Gly Trp Ser Tyr Leu Asn Thr Val Glu Arg Trp Asp Pro Gln Ala 230 235 Arg Gln Trp Asn Phe Val Ala Thr Met Ser Thr Pro Arg Ser Thr Val 250 Gly Val Ala Val Leu Ser Gly Lys Leu Tyr Ala Val Gly Gly Arg Asp 265 260 Gly Ser Ser Cys Leu Lys Ser Val Glu Cys Phe Asp Pro His Thr Asn 280 Lys Trp Thr Leu Cys Ala Gln Met Ser Lys Arg Arg Gly Gly Val Gly 295 300 Val Thr Trp Asn Gly Leu Leu Tyr Ala Ile Gly Gly His Asp Ala 310 315 Pro Ala Ser Asn Leu Thr Ser Arg Leu Ser Asp Cys Val Glu Arg Tyr 325 330 Asp Pro Lys Thr Asp Met Trp Thr Ala Val Ala Ser Met Ser Ile Ser 345 Arg Asp Ala Val Gly Val Cys Leu Leu Gly Asp Lys Leu Tyr Ala Val 360 Gly Gly Tyr Asp Gly Gln Ala Tyr Leu Asn Thr Val Glu Ala Tyr Asp 375 380 Pro Gln Thr Asn Glu Trp Thr Gln Val Ala Pro Leu Cys Leu Gly Arg 390 400 Ala Gly Ala Cys Val Val Thr Val Lys Leu 405 <210> 5 <211> 1644 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1644) <400> 5 atg ctg cgg tac ctg gag acg gca gac tac gcc atc cgc gag gag atc 48 Met Leu Arg Tyr Leu Glu Thr Ala Asp Tyr Ala Ile Arg Glu Glu Ile 1 10

11 ·

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			_		atc Ile									_		144
	_	Glu			tgg Trp		_					_			_	192
					tat Tyr 70	-	-								_	240
					gag Glu											288
					ctg Leu		-									336
	_			-	ctc Leu			-			-	-	_		-	384
_			-	-	ctg Leu					-						432
					acc Thr 150											480
					gtg Val											528
					gcc Ala											576

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											_	ggc Gly		672
												acc Thr		720
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_	-		-	-	-		_	Αla		•	 -	999 Gly		816
								-			_	ctg Leu		864
				_			-				 _	atc Ile		912
					-		_	_		-		tgt Cys	-	960
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		_	_		_		-	_				ggc Gly		1056
												cac His	-	1104

	gac Asp 370													1152
	gtg Val				-		-	-					_	1200
_	cgg Arg		_	_		-	-	-			-	 		1248
-	ggc Gly	-	_	-			-	_						1296
	ttc Phe					_		-	_	-		_	_	1344
	aag Lys 450						_							1392
	aac Asn		_	_	-	-	-		-	_	-	-		1440
	ggc Gly			_	_			_						1488
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14

1644

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			260					265					270		
Leu	Leu	Val 275	Asp	Val	Phe	Asp	Gly 280	Pro	Ala	Ala	Gln	Pro 285	Ser	Leu	Gly
Pro	Thr 290	Pro	Glu	Glu	Ala	Phe 295	Leu	Ser	Pro	Gly	Pro 300	Glu	Asp	Ile	Gly
Pro 305	Pro	Ile	Pro		Ala 310	Asp	Glu	Leu	Leu	Asn 315	Lys	Phe	Val	Cys	Lys 320
Asn	Asn	Gly	Val	Leu 325	Phe	Glu	Asn	Gln	Leu 330	Leu	Gln	Пe	Gly	Val 335	Lys
Ser	Glu	Phe	Arg 340	Gln	Asn	Leu	Gly	Arg 345	Met	Tyr	Leu	Phe	Tyr 350	Gly	Asn
Lys	Thr	Ser 355	Val	Gln	Phe	Gln	Asn 360	Phe	Ser	Pro	Thr	Val 365	Val	His	Pro
Gly	Asp 370	Leu	Gln	Thr	Gln	Leu 375	Ala	Val	Gln	Thr	Lys 380	Arg	Val	Ala	Ala
G1n 385	Val	Asp	Gly	Gly	Ala 390	Gln	Val	G1n	Gln	Va1 395	Leu	Asn	Ile	Glu	Cys 400
Leu	Arg	Asp	Phe	Leu 405	Thr	Pro	Pro	Leu	Leu 410	Ser	Val	Arg	Phe	Arg 415	Tyr
Gly	Gly	Ala	Pro 420	Gln	Ala	Leu	Thr	Leu 425	Lys	Leu	Pro	Val	Thr 430	Įlе	Asn
Lys	Phe	Phe 435		Pro	Thr	Glu	Met 440	Ala	Ala	Gln	Asp	Phe 445	Phe	Gln	Arg
Trp	Lys 450	Gln	Leu	Ser	Leu	Pro 455	Gln	Gln	Glu	Ala	G1n 460	Lys	Ile	Phe	Lys
A1a 465	Asn	His	Pro	Met	Asp 470	Ala	Glu	Val	Thr	Lys 475	Ala	Lys	Leu	Leu	G1y 480
Phe	Gly	Ser	Ala	Leu 485	Leu	Asp	Asn	Val	Asp 490	Pro	Asn	Pro	Glu	Asn 495	Phe
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Leu	Arg	Leu 515	Glu	Pro	Asn	Ala	G1n 520	Ala	Gln	Met	Tyr	Arg 525	Leu	Thr	Leu
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tcc atc atg att ggt gta aaa cca tgt att gac aaa agt gtt atg gaa Ser Ile Met Ile Gly Val Lys Pro Cys Ile Asp Lys Ser Val Met Glu

155

150

145

17

_	-	_	_	-		tta Leu						!	528
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Ser	Ser	Asp	Arg	Cys 165	Ala	Leu	Ser	Ser	Pro 170	Ser	Leu	Ala	Phe	Thr 175	Pro	
Pro	Пe	Lys	Thr 180	Leu	Gly	Thr	Pro	Thr 185	Gln	Pro	Gly	Ser	Thr 190	Pro	Arg	
Пe		Thr 195	Met	Arg	Pro	Leu	A1a 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	He	Ser	Asp 215	Arg	Gln	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	
Leu 225	Val	Ser	Lys	Ala	Met 230	Glu	Tyr	Met	Phe	G1y 235	Trp					
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	-			-	-	-	-		_		aaa Lys 60					192
											aga Arg					240

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19

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						act Thr	-			-	-		_		288
-			-	_	-	aat Asn	-				_		-		336
		-		-		cat His	-			-		•	-	_	384
_	-					tat Tyr 135					_			-	432
				_		att Ile	_			-	-		-		480
	-			-		aaa Lys	-	•					-		528
						aaa Lys									576
_	_		_	-		ctc Leu	-		-						624
	aag Lys 210		taa *												636
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Asp	Gln	Met 35	Ser	Asn	Glu	Glu	Leu 40	Tyr	Asp	Asn	Ļeu	Leu 45	Ser	Cys	Ser		
His	Arg 50	Thr	His	Val	Val	Ala 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	Asp	Leu		
65	Val				70	-				75					80		
	Thr			85				·	90			,		95	•		
	Ile		100					105					110				
	Pro	115					120					125					
	Ala 130					135					140						
145	Phe				150					155					160		
	Val			165					170					175			
	Leu		180					185					190				
	Lys Lys 210	195	Lys	АЗР	Tyi		200	Tie		Arg	PTU	205	116	Tie	Lys		
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	tcc Ser															•	+0
	ccg Pro					_										•	96

	20				25					30			
		_			-				-	_	ctc Leu	•	144
									-	-	ggc Gly	_	. 192
											agc Ser		240
											cgt Arg 95		288
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		_	-			_		-	-	_	gag Glu	-	432
											tgc Cys		. 480
											gag Glu 175		528
				-			-		-		gta Val		576
											gat Asp		624

22

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<213> Homo sapiens

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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro 100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val 165 170 175

Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro 180 185 190

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Lys Val Lys Lys Glu Arg Asp Pro 210 215

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23

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24

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Leu Thr Lys Phe Asn Lys Glu Asn Asn Cys Val Leu Pro His Ser Lys
Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
    50
                        55
Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro-
                                        75
Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr
                                105
Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
                            120
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1				5					10					15			
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-	-		-			-	-					ttt Phe 45	-			. 1	44
		**		_		_	-					tgg Trp				1	92
						-						ctg Leu				2	40
					-				-			cac His		_	-	2	88
				-			-				-	cag Gln	-	_	-	3	36
					_	-		-	-	_		ggc Gly 125	-			3	84
									_			cag Gln			_	4	32
	-			-			-	-	_	-		acc Thr	_			4	80
												cgc Arg				5	28
					-	-			-	-		gga Gly				5	76

26

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180 185 190 gcc ctg agt cta agg tcc agc aca aac ccg gca gat tcc cgg aca gag 624 Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 195 200 get tet gag gat gae atg gga gae aaa get eec aag agg gee aaa eec 672 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 210 215 220 atc aaa aaa gcg ccc aaa gct gag cca ctg gct tcc aag aca ctg aag 720 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 225 230 235 240 acc cgg ccc aag aag acc tct ggc ggg ggc gac tca gct tga 765 Thr Arg Pro Lys Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala * 245 250 <210> 16 <211> 254 <212> PRT <213> Homo sapiens <400> 16 Met Val Ser Trp Ile Ile Ser Arg Leu Val Val Leu Ile Phe Gly Thr 5 Leu Tyr Pro Ala Tyr Ser Ser Tyr Lys Ala Val Lys Thr Lys Asn Val 25 Lys Glu Tyr Val Lys Trp Met Met Tyr Trp Ile Val Phe Ala Phe Phe Thr Thr Ala Glu Thr Leu Thr Asp Ile Val Leu Ser Trp Phe Pro Phe 55 60 Tyr Phe Glu Leu Lys Ile Ala Phe Val Ile Trp Leu Leu Ser Pro Tyr 65 70 75 80 Thr Lys Gly Ser Ser Val Leu Tyr Arg Lys Phe Val His Pro Thr Leu 90 Ser Asn Lys Glu Lys Glu Ile Asp Glu Tyr Ile Thr Gln Ala Arg Asp 105 110 Lys Ser Tyr Glu Thr Met Met Arg Val Gly Lys Arg Gly Leu Asn Leu 115 120 125 Ala Ala Asn Ala Ala Val Thr Ala Ala Ala Lys Gly Gln Gly Val Leu

135

Ser Glu Lys Leu Arg Ser Phe Ser Met Gln Asp Leu Thr Leu Ile Arg

145					150					155					160	
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Ser	Pro	Gly	Ser 180	Leu	Leu	Asp	Thr	Ile 185	Glu	Asp	Leu	Gly	Asp 190	Asp	Pro	
Ala	Leu	Ser 195	Leu	Arg	Ser	Ser	Thr 200	Asn	Pro	Ala	Asp	Ser 205	Arg	Thr	Glu	
Ala	Ser 210	Glu	Asp	Asp	Met	Gly 215	Asp	Lys	Ala	Pro	Lys 220	Arg	Ala	Lys	Pro	
Ile 225	Lys	Lys	Ala	Pro	Lys 230	Ala	Glu	Pro	Leu	A1 a 235	Ser	Lys	Thr	Leu	Lys 240	
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				gac Asp												96
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		-	-	ctc Leu	-	_				_					-	192

	cga Arg				-	-			-						-		240
	cct Pro				-												288
_	ctc Leu																336
	gag Glu																384
	cta Leu 130				_	_	taa *										408
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_	Ala	Asn	Xaa 20	-	Thr	Ala	Asn	Lys 25		Gly	Thr	Tyr	G1n 30		Ala		
Ile	Val	Ala 35		His	His	Gly	Ile 40		Phe	Tyr	Val	A1a 45		Pro	Ser	•	
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Glu 65	Aṛg	Pro	Gly	Gln	G1u 70		Thr	Asp	Val	Asn 75		Val	Arg	Ile	Ala 80		
	Pro	Gly	Ile	G1y 85		Trp	Asn	Pro	A1a 90		Asp	Val	Thr	Pro 95			

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			agt Ser				-				_		_	_		384
	-		ttt Phe			-										432
	-	_	ctg Leu	_					_	_	_	_	_	_	_	480
			ggc Gly		-	_						-				528
			gag Glu 180		_			_			_		_		-	576
			cag Gln				_	-				-				624
			ctg Leu													672
			cat His		_	_			_		-		_			720
			acc Thr													768
			gga Gly 260				Asn									816
-	gaa Glu		tga *													828

31

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32

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Glu	Phe	Glu 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr	
					999 Gly											432
-	_		•		gaa Glu 150		-								•	480
	_		_	-	caa Gln	-									-	528
	_			_	gaa Glu	_	-						-		-	[.] 576
					ttc. Phe											624
-					cca Pro				-				-	_	-	672
		-	_		gag Glu 230	-		-			_					720
-		-			ggt Gly						-				•	768
					atc Ile	_			-							816
					cag Gln		_	-								864
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc	912

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Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu	
			_	_										tgt Cys		960
			_	_			-	-			-		-	cac His 335	_	1008
					_	_			-	-			_	ggc Gly	_	1056
			-	_				_	-		_	_		cac His	-	1104
					-	_			_		_	_		agc Ser	-	1152
														agg Arg		1200
											_		_	gcc Ala 415		1248
							-			_			-	tgc Cys		1296
														cac His	_	1344
														ggc Gly		1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	Gln	Arg	Ser	His	Thr 480	
	gag Glu					_								-	-	1488
	tcc Ser	_		_	_				-		-					1536
	aag Lys															1584
	cgc Arg 530							-				tga *				1623
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Met 1	Glu	Arg	Glu	Ala 5	Leu	Pro	Trp	Gly	Leu 10	Glu	Pro	Gln	Asp	Val 15	Gln	
Ser	Ser	Asp	G1u 20	Met	Arg	Ser	Pro	G1u 25	Gly	Asn	Leu	Arg	G1y 30	Asn	Met	
Ser	Glu			Glu	Glu	Glu	Ile 40		Gln	Gln	Glu	G1y 45		Gly	Asp	
Tvr		1					70						_		_	
. , .	Glu 50	35 Val	Glu	Glu	Пе		Phe	Gly	Leu	Glu		Gln	Ser	Pro	Gly	
Phe	Glu 50 Glu	Val			Pro	55		•		Gln	60	•			Glu	
Phe 65	50	Val Pro	G1n	Ser	Pro 70	55 G1u	Phe	Glu	Pro	G1n 75	60 Ser	Pro	Arg	Phe	Glu 80	

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•			100					105					110		
Glu	Phe	G1u 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr
Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
G1u 145	Ser	Ser	Arg	Tyr	Glu 150	Ser	Gln	Asn	Thr	G1u 155	Leu	Lys	Thr	Gln	Ser 160
Pro	Glu	Phe	Glu	Ala 165	Gln	Ser	Ser	Lys	Phe 170	Gln	Glu	Gly	Ala	Glu 175	Met
Leu	Leu	Asn	Pro 180	Xaa	Glu	Lys	Ser	Pro 185	Leu	Asn	IJе	Ser	Val 190	Gly	Val
		195	·				200		Phe			205			•
Asp	Leu 210	Pro	Ile	Gly	Pro	Pro 215	Phe	Glu	Met	Pro	Thr 220	Gly	Ala	Leu	Leu
225					230				Asn	235		-			240
			-	245	-				G1y 250	_				255	
			260					265	Cys				270		
		275					280		Ile			285		·	
	290					295			Phe		300				
305				_	310			-	Glu	315		-	-	•	320
				325					Ser 330					335	
_			340	·		•		345	Lys	•			350	•	_
Ala	Phe	G1 <i>y</i> 355	Asp	Ser	Ser	Tyr	Leu 360	Leu	Arg	His	Gln	Arg 365	Thr	His	Ser
	370					375			Cys		380				
Asn 385	Ser	Ser	Leu	Arg	Ser 390	His	Gln	Arg	Val	His 395	Thr	Gly	G1n	Arg	Pro 400
Phe	Ser	Cys	Gly	Ile 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
He	Pro	His	Ala 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	G1 <i>y</i> 435	Lys	Arg	Phe	Gly	G1n 440	Ser	Ser	Val	Leu	Ala 445	Пe	His	Ala
Arg	Thr	His	Leu	Pro	Gly	Arg	Thr	Tyr	Ser	Cys	Pro	Asp	Cys	Gly	Lys

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	450					455					460					
Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	Gln	Arg	Ser	His	Thr 480	
Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg	
Ser	Ser	Thr	Leu 500	Leu	Gln	His	His	Arg 505	۷a٦	His	Ser	Gly	Glu 510	Arg	Pro	
Tyr	Lys	Cys 515	Asp	Asp	Cys	Gly	Lys 520	Ala	Phe	Ser	Gln	Ser 525	Ser	Asp	Leu	
Ile	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg	Arg 540		-	`		
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	<2	220> 221> 222>		(4	1 32)											
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												gag Glu				96
_		_		_	-		_	_	-			atc Ile 45		_	-	144
												gtg Val				192
_	-		-				-	-				ctg Leu		_		240
-	-		-						-			ttt Phe	ccg Pro			288

38

85 90 95 336 aga atc atc acc acq gcg gtg gac aag cgg gtc aat gac ctt ttc cgc Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly * 130 135 140 <210> 24 <211> 143 <212> PRT <213> Homo sapiens <400> 24 . Met Glu Pro Ala Leu Arg Ala Val Cys Lys Asp Val Arg Ile Gly Thr 10 Ile Leu Ile Gln Thr Asn Gln Leu Thr Gly Glu Pro Glu Leu His Tyr Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp 40 45 Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 85 90 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 120 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly

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<211> 912

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<213> Homo sapiens

135

39

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							ttc Phe	-						_	_	96	
-					-		ccc Pro 40									144	
		_	-	-	_	_	cag Gln		_			-				192	
-			-		_	_	gaa Glu	_	-	-	_			_		240	
-				-			tac Tyr									288	
					_	_	gtg Val	_	_			-			_	336	
-	_					_	acc Thr 120			-			-	-		384	
-		-	-		-		cac His	_						-		432	
							ttc Phe									480	

40

145					150					155				160	
	_	-	gcc Ala				-	-		-		_	_	_	528
	_	_	gga Gly 180	_						_	_			-	576
-		_	gag Glu	_			_							-	624
			999 Gly			-			-	-		-			672
			atc Ile												720
	_		ccc Pro		-			-				_	_	•	768
-		_	ggc Gly 260					-			_	 			816
			gac Asp												864
-	-	_	gcc Ala	-		_	-	-	-	-				tga *	912

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<211> 303

<212> PRT

<213> Homo sapiens

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<210> 27

<211> 795

<212> DNA

<213> Homo sapiens

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						-	-		_		atc Ile		96
											aat Asn		144
											gaa Glu		192
		-	_		_			-		_	gaa Glu		240
											aaa Lys 95		288
											ata Ile	_	336
											gat Asp		384
						_	-				gtt Val		432

	130					135					140					
_			-			_		_	-	-			_	aat Asn		480
	_		-					-		-	-	_	_	aag Lys 175	•	528
														ttc Phe		576
		_	_	-	-					_			-	gtg Val	-	624
				_										aca Thr		672
_		_		_		_		_		_	_	_		tta Leu	-	720
			-	-	-		-	-	-	-	-	-	-	tcc Ser 255		768
				-	ctt Leu			taa *								795
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<210> 29

<211> 711

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<213> Homo sapiens

<220>

<221> CDS

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<222> (1)...(711)

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			-	-	tac Tyr	_				_							96
					ctc Leu											:	144
		-			tat Tyr	_	-	_			-	-			-		192
				-	ctg Leu 70			-							-		240
-	-	-			ttg Leu				-				-			ć	288
-			-	-	ttg Leu						-	-				;	336
				_	agt Ser					-			-				384
	_	_			gtt Val	-										4	432
					gat Asp 150											4	480
cag	ctg	gct	gga	ctg	aca	ttg	ttg	aca	aac	atg	act	gtt	acc	aat	gac	į	528

G1n	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp	
				•		agt Ser							-			576
						acg Thr							_		-	624
			-			gcc Ala 215	-		_				-	-		672
_						tcc Ser		_		-	_	tag *				711
	<2 <2	210> 211> 212> 213>	236	sap	oiens	5	٠									
Mat		<00	30													
1		Clv		Λνα	614	۸٦,	Clv	Tnn	V-1	۸٦٠	۸٦٠	Clv	t ou	Lou	Lou	
	diy	Gly		Arg 5	Gly	Ala	Gly	Trp	Val 10	Ala	Ala	Gly	Leu	Leu 15	Leu	
			Pro	5		Ala Cys	-	,	10					15		
Gly	Ala	Gly	Pro Ala 20	5 Cys	Tyr		Ile	Tyr 25	10 Arg	Leu	Thr	Arg	G1y 30	15 Arg	Arg	
Gly Arg	Ala Gly Thr	Gly Asp 35	Pro Ala 20 Arg	5 Cys Glu	Tyr Leu	Cys	Ile Ile 40	Tyr 25 Arg	10 Arg Ser	Leu Ser	Thr Lys	Arg Ser 45	Gly 30 Ala	15 Arg Glu	Arg Asp	
Gly Arg Leu Lys	Ala Gly Thr 50	Gly Asp 35 Asp	Pro Ala 20 Arg Gly	5 Cys Glu Ser	Tyr Leu Tyr Leu	Cys Gly Asp	Ile Ile 40 Asp	Tyr 25 Arg Val	10 Arg Ser Leu	Leu Ser Asn Asp	Thr Lys Ala 60	Arg Ser 45 Glu	Gly 30 Ala Gln	15 Arg Glu Leu	Arg Asp Gln Glu	
Gly Arg Leu Lys 65	Ala Gly Thr 50 Leu	Gly Asp 35 Asp Leu	Pro Ala 20 Arg Gly Tyr	5 Cys Glu Ser Leu Thr	Tyr Leu Tyr Leu 70	Cys Gly Asp 55	Ile Ile 40 Asp Ser	Tyr 25 Arg Val	10 Arg Ser Leu Glu Ala	Leu Ser Asn Asp 75	Thr Lys Ala 60 Pro	Arg Ser 45 Glu Val	Gly 30 Ala Gln Ile	15 Arg Glu Leu Ile Asn	Arg Asp Gln Glu 80	
Gly Arg Leu Lys 65 Arg	Ala Gly Thr 50 Leu Ala	Gly Asp 35 Asp Leu Leu	Pro Ala 20 Arg Gly Tyr Ile Arg	5 Cys Glu Ser Leu Thr 85	Tyr Leu Tyr Leu 70 Leu	Cys Gly Asp 55 Glu	Ile Ile 40 Asp Ser Asn	Tyr 25 Arg Val Thr Asn	10 Arg Ser Leu Glu Ala 90	Leu Ser Asn Asp 75 Ala	Thr Lys Ala 60 Pro	Arg Ser 45 Glu Val	Gly 30 Ala Gln Ile Val	15 Arg Glu Leu Ile Asn 95	Arg Asp Gln Glu 80 Gln	
Gly Arg Leu Lys 65 Arg	Ala Gly Thr 50 Leu Ala Ile	Gly Asp 35 Asp Leu Leu Ile	Pro Ala 20 Arg Gly Tyr Ile Arg 100	5 Cys Glu Ser Leu Thr 85 Glu	Tyr Leu Tyr Leu 70 Leu Leu	Cys Gly Asp 55 Glu Gly	Ile Ile 40 Asp Ser Asn Gly	Tyr 25 Arg Val Thr Asn Ile 105	10 Arg Ser Leu Glu Ala 90 Pro	Leu Ser Asn Asp 75 Ala Ile	Thr Lys Ala 60 Pro Phe	Arg Ser 45 Glu Val Ser Ala	Gly 30 Ala Gln Ile Val Asn 110	15 Arg Glu Leu Ile Asn 95 Lys	Arg Asp Gln Glu 80 Gln Ile	

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Ser 145	Gln	Val	Cys	Glu	Asp 150	Val	Phe	Ser	Gly	Pro 155	Leu	Asn	Ser	Ala	Val 160	
Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp	
His	Gln	His	Met 180	Leu	His	Ser	Tyr	Ile 185	Thr	Asp	Leu	Phe	Gln 190	Val	Leu	
Leu	Thr	Gly 195	Asn	Gly	Asn	Thr	Lys 200	Val	Gln	Val	Leu	Lys 205	Leu	Leu	Leu	
Asn	Leu 210	Ser	Glu	Asn	Pro	Ala 215	Met	Thr	Glu	Gly	Leu 220	Leu	Arg	Ala	Gln	
Va1 225	Asp	Ser	Ser	Phe	Leu 230	Ser	Leu	Met	Thr	A1a 235	Thr					
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		100>									-					
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	ccg Pro			-	-			-				-	-		-	96
	gtc Val		-		_	_	_		-	-		-	_			144
	ctg Leu 50			_			_	_			-		-	_	-	192
	tgg Trp	-	-	-	-				-					_	_	240
cag																

Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp	
				gag Glu						-	-				•	336
				gaa Glu			-			-				_	-	384
				gcc Ala											_	432
-		-		att Ile	-				_		_				•	480
	-			cca Pro 165			-		-	-	-		_			528
				tgg Trp										-	-	576
				ttc Phe												624
				gtc Val											-	672
	-	-	_	ctt Leu	_			_								720
				atc Ile 245												768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	999	tac	atg	aat	gtg	816

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Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
											agg Arg					864
											cgc Arg 300			-		912
							_			-	aag Lys				•	960
											gac Asp					1008
											ggg Gly					1056
									-	-	atc Ile					1104
				-			-				tcg Ser 380	_	_		-	1152
						-			_		tac Tyr				_	1200
						-	-		-	-	gtg Val			-	_	1248
											gag Glu					1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

50

Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440	Trp	Asp	Leu	Ile	Tyr 445	Leu	Gly	Arg	
_						aag Lys 455							_	_		1392
						tcc Ser							-	_	-	1440
	-	-		-	_	ctg Leu	_	-		-		_	-	-	-	1488
-			-			ctg Leu			_		_	-				1536
	_		_	-		ttc Phe				-	-		-			1584
						gcc Ala 535										1632
		_	_	-		aca Thr					-	-	-	_		1680
_			_		-	ggc Gly			-		-	-	-		-	1728
tgg Trp	acc Thr	tga *														1737

<210> 32

<211> 578

<212> PRT

<213> Homo sapiens

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Met Leu Ala Ser Leu Trp Glu Met Glu Ile Ser Gly Arg Val Val Asp
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Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
        355
                            360
                                                365
Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
    370
                        375
                                            380
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
                   390
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
                                425
Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
                        455
                                            460
Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
                   470
                                        475
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
                                    490
               485
Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
                                505
Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
                            520
                                                525
Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
                        535
                                            540
Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Ser Gly
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                                        555
Arg Leu Ile Ser Trp Ser Gly Ser Gln Lys Thr Leu Arg Ser Pro Ala
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Trp Thr
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<211> 1152

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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<400> 33

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96	-	gca Ala	_					-					_			
144		cat His		-	-		_	_	-		-			-		-
192	-	gca Ala	-		-	-	-	_								
240	-	cag Gln	-	-	Τ.		-	_		-		_	-	-		
288	-	att Ile 95					_		-				-	-	_	
336	-	ttg Leu				-	-		_	-	-			_	-	
384		aga Arg					_	-	-	-	-	_	_			
432		agc Ser	_		-				_	_			-			
480	-	cca Pro				_			_						-	-
528		atg Met 175			_	-				-	_		_			
. 576	gtc	gca	att	gaa	ggt	aaa	ttt	gaa	gaa	gca	atg	gga	ctt	gtg	tat	atg

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Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	Glu 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val	
													_	gat Asp	_	624
_						-	-	_	_	-		-	_	atc Ile		672
-	_	_	-						-			_		act Thr		720
		-		_	_					-	-			gaa Glu 255		768
	-			-							-			gat Asp		816
														tca Ser		864
	-			_			-			_	_	_		cca Pro		912
				-		-	-			-		-	_	gac Asp		960
	_	-	-	-	-		_			-			-	ttt Phe 335	_	1008
														agc Ser	_	1056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 atg agt atg act act gat gac ttt gta aaa atg ttt tca ggg aac taa 1152 Met Ser Met Thr Thr Asp Asp Phe Val Lys Met Phe Ser Gly Asn * 370 375 <210> 34 <211> 383 <212> PRT <213> Homo sapiens <400> 34 Met Leu Pro Asn Thr Gly Arg Leu Ala Gly Cys Thr Val Phe Ile Thr Gly Ala Ser Arg Gly Ile Gly Lys Ala Ile Ala Leu Lys Ala Ala Lys 25 Asp Gly Ala Asn Ile Val Ile Ala Ala Lys Thr Ala Gln Pro His Pro Lys Leu Leu Gly Thr Ile Tyr Thr Ala Ala Glu Glu Ile Glu Ala Val 55 60 Gly Gly Lys Ala Leu Pro Cys Ile Val Asp Val Arg Asp Glu Gln Gln 70 Ile Ser Ala Ala Val Glu Lys Ala Ile Lys Lys Phe Gly Gly Ile Asp 90 Ile Leu Val Asn Asn Ala Ser Ala Ile Ser Leu Thr Asn Thr Leu Asp 100 105 Thr Pro Thr Lys Arg Leu Asp Leu Met Met Asn Val Asn Thr Arg Gly 120 Thr Tyr Leu Ala Ser Lys Ala Cys Ile Pro Tyr Leu Lys Lys Ser Lys 135 Val Ala His Ile Leu Asn Ile Ser Pro Pro Leu Asn Leu Asn Pro Val 150 155 Trp Phe Lys Gln His Cys Ala Tyr Thr Ile Ala Lys Tyr Gly Met Ser 170 165 Met Tyr Val Leu Gly Met Ala Glu Glu Phe Lys Gly Glu Ile Ala Val 185 Asn Ala Leu Trp Pro Lys Thr Ala Ile His Thr Ala Ala Met Asp Met 200 Leu Gly Gly Pro Gly Ile Glu Ser Gln Cys Arg Lys Val Asp Ile Ile 215 220 Ala Asp Ala Ala Tyr Ser Ile Phe Gln Lys Pro Lys Ser Phe Thr Gly 225 230 235 240

Asn	Phe	Val	Пе	Asp 245	Glu	Asn	Пe	Leu	Lys 250	Glu	Glu	Gly	Пe	G1u 255	Asn	
Phe	Asp	Val	Tyr 260	Ala	IJе	Lys	Pro	G1y 265	His	Pro	Leu	Gln	Pro 270	Asp	Phe	
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	Ala 280	Val	Ser	Lys	Lys	Va1 285	Glu	Ser	Thr	
Gly	Ala 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys	Leu	G1n 300	Leu	Gln	Pro	Lys	
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315	Пe	Val	Lys	Asp	Ser 320	
Leu	Ser	Asp	Asp	Va1 325	Val	Lys	Ala	Thr	G1n 330	Ala	Ile	Tyr	Leu	Phe 335	Glu	
	Ser	_	340	·	-			345			·		350		·	
-	Gly	355		-		_	360			·		365	·		Val	
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn		
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	<2	222>	(1).	c_fea (1 A.T.	1371))										
	<4 999 Gly		tgc													48
	tgc Cys			_		_		_	-	_	_	_		-	-	96
-	aac Asn				_	-									_	144

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gtg Val 50												192
tac Tyr												240
ctg Leu			-	-	-		_			-	_	288
tac Tyr			-	_		-						336
ctc Leu			_						 -	-		384
aat Asn 130				-		_		_	 			432
ggt Gly												480
ttc Phe		 							_	-		528
ctc Leu												576
gag Glu			-	_			-					624
ctc Leu 210												672

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				ccc Pro 230						_	_			720
				ttc Phe								_	_	768
			-	gcc Ala				-	_	_	-	-	_	816
				acc Thr	_	-				_	Leu		•	864
				tgc Cys						_	-			912
				ggc Gly 310										960
				ggc Gly					-	_				1008
_	-	_		tca Ser	_		_	_		•	_	_	_	1056
				cct Pro										1104
				gag G1u										1152
				tcc Ser 390										1200

59

ctg cac gtc atg atg acg ctc acc aac tgg tac aag ccc ggt gag acc 1248 Leu His Val Met Met Thr Leu Thr Asn Trp Tyr Lys Pro Gly Glu Thr 405 410 1296 cgg aag atg atc agc acg tgg acc gcc gtg tgg gtg aag atc tgt gcc Arg Lys Met Ile Ser Thr Trp Thr Ala Val Trp Val Lys Ile Cys Ala 420 425 430 ago tgg goa ggg ctg ctc ctc tac ctg tgg acc ctg gta gcc cca ctc 1344 Ser Trp Ala Gly Leu Leu Leu Tyr Leu Trp Thr Leu Val Ala Pro Leu 435 440 ctc ctg cgc aac cgc gac ttc agc tga 1371 Leu Leu Arg Asn Arg Asp Phe Ser * 450 455 <210> 36 <211> 456 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(456) <223> Xaa = Any Amino Acid <400> 36 Met Gly Ala Cys Leu Gly Ala Cys Ser Leu Leu Ser Cys Ala Ser Cys Leu Cys Gly Ser Ala Pro Cys Ile Leu Cys Ser Cys Cys Pro Ala Ser 25 Arg Asn Ser Thr Val Ser Arg Leu Ile Phe Thr Phe Phe Leu Phe Leu Gly Val Leu Val Ser Ile Ile Met Leu Ser Pro Gly Val Glu Ser Gln 55 60 Leu Tyr Lys Leu Pro Trp Val Cys Glu Glu Gly Ala Gly Ile Pro Thr 70 75 Val Leu Gln Gly His Ile Asp Cys Gly Ser Leu Leu Gly Tyr Arg Ala 90 Val Tyr Arg Met Cys Phe Ala Thr Ala Ala Phe Phe Phe Phe Thr 105 Leu Leu Met Leu Cys Val Ser Ser Ser Arg Asp Pro Arg Ala Ala Ile

			115					120					125			•
	Gln	Asn 130	Gly	Phe	Trp	Phe	Phe 135	Lys	Phe	Leu	Ile	Leu 140	Val	Gly	Leu	Thr
	Val 145	Gly	Ala	Phe	Tyr	Ile 150	Pro	Asp	Gly	Ser	Phe 155	Thr	Asn	Ile	Trp	Phe 160
	Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	Ile	Leu	Ile	Gln	Leu 175	۷a۱
	Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185	Asn	Gln	Arg	Trp	Leu 190	Gly	Lys
	Ala	Glu	Glu 195	Cys	Asp	Ser	Arg	Ala 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
		210			-	Leu	215					220				
	Met 225	Tyr	Tyr	Thr	Glu	Pro 230	Ser	Gly	Cys	His	G1u 235	Gly	Lys	Val	Phe	11e 240
	Ser	Leu	Asn	Leu	Thr 245	Phe	Cys	Val	Cys	Va1 250	Ser	Ile	Ala	Ala	Va1 255	Leu
	Pro	Lys	Val	G1n 260	Asp	Ala	Gln	Pro	Asn 265	Ser	Gly	Leu	Leu	G1n 270	Ala	Ser
	Val	Ile	Thr 275	Leu	Tyr	Thr	Met	Phe 280	Val	Thr	Trp	Ser	A1 a 285	Leu	Ser	Ser
	He	Pro 290	Glu	Gln	Lys	Cys	Asn 295	Pro	His	Leu	Pro	Thr 300	Gln	Leu	Gly	Asr
	305					Gly 310			-	Ť	315			•	•	320
					325	Gly				330					335	
				340		Ser			345					350		
			355	-		Pro		360	,				365			
		370				Glu	375				•	380			·	
	385					Ser 390					395					400
	Leu	His	Val	Met	Met 405	Thr	Leu	Thr	Asn	Trp 410	Tyr	Lys	Pro	Gly	G1u 415	Thr
	Arg	Lys	Met	Ile 420	Ser	Thr	Trp	Thr	A1a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
•	Ser	Trp	A1a 435	Gly	Leu	Leu	Leu	Tyr 440	Leu	Trp	Thr	Leu	Va1 445	Ala'	Pro	Leu
	Leu	Leu 450	Arg	Asn	Arg	Asp	Phe 455	Ser								

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61

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	130					135					140					
-	_						_	cca Pro		_					•	480
			-		-	_		acc Thr						_		528
_					_	-	-	gaa Glu 185				_		_	-	576
	-						-	ata Ile			-	-	_	-	-	624
								cag Gln								672
-	-	-	-					caa Gln	-							720
				-	-			tta Leu		-				-		768
	-	_	Tyr	Ala	Пe		Pro	ggt Gly 265	His	Pro	Leu			-		816
		-	-			-	_	gtt Val	-	-			-			864
				-			_	gag Glu								912
	_			-		-	-	aca Thr		_			_	-		960

63

305	310	315	320
	Val Lys Ala Thr 0	caa gca atc tat ctg Gln Ala Ile Tyr Leu 330	•
		ttt ctt gat ctg aaa Phe Leu Asp Leu Lys 350	
ggt ggg aat gtc gga Gly Gly Asn Val Gly 355			
atg agt atg act act Met Ser Met Thr Thr 370		aaa atg ttt tca ggg _ys Met Phe Ser Gly 380	
aaa cca aca atg gca Lys Pro Thr Met Ala 385		aaa ttg aag att aaa Lys Leu Lys Ile Lys 395	••
atg gcc cta gca atc Met Ala Leu Ala Ile 405	Lys Leu Glu Lys L	eu Met Asn Gln Met	-
aga ctg tga Arg Leu *			1257

<210> 38

<211> 418

<212> PRT

<213> Homo sapiens

<400> 38

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Asp Gly Ala Asn Ile Val Ile Ala Ala Lys Thr Ala Gln Pro His Pro 35 40 45
Lys Leu Leu Gly Thr Ile Tyr Thr Ala Ala Glu Glu Ile Glu Ala Val

	50					55					60				
Gly 65	Gly	Lys	Ala	Leu	Pro 70	Cys	Ile	Val	Asp	Val 75	Arg	Asp	Glu	Gln	G1n 80
Ile	Ser	Ala	Ala	Va1 85	Glu	Lys	Ala	Ile	Lys 90	Lys	Phe	Gly	Gly	Ile 95	Asp
He	Leu	Val	Asn 100	Asn	Ala	Ser	Ala	Ile 105	Ser	Leu	Thr	Asn	Thr 110	Leu	Asp
Thr	Pro	Thr 115	Lys	Arg	Leu	Asp	Leu 120	Met	Met	Asn	Val	Asn 125	Thr	Arg	Gly
Thr	Tyr 130	Leu	Ala	Ser	Lys	Ala 135	Cys	Ile	Pro	Tyr	Leu 140	Lys	Lys	Ser	Lys
Val 145	Ala	His	Ile	Leu	Asn 150	He	Ser	Pro	Pro	Leu 155	Asn	Leu	Asn	Pro	Val 160
Trp	Phe	Lys	Gln	His 165	Cys	Ala	Tyr	Thr	Ile 170	Ala	Lys	Tyr	Gly	Met 175	Ser
	-		180	-				185		-	_		190	Ala	
Asn	Ala	Leu 195	Trp	Pro	Lys	Thr	Ala 200	Пe	His	Thr	Ala	A1a 205	Met	Asp	Met
Leu	Gly 210	Gly	Pro	Gly	Ile	Glu 215	Ser	Gln	Cys	Arg	Lys 220	Val	Asp	Ile	Ile
225					230				-	235	_				240
				245					250					G1u 255	
	•		260			-		265					270	Asp	
		275		•			280					285		Ser	
	290					295					300			Pro	
305					310					315				Asp	320
				325					330					Phe 335	
			340					345					350	Ser	
Gly	Gly	Asn 355	Val	Gly	Tyr	Gly	G1u 360	Pro	Ser	Asp	Gln	A1a 365	Asp	Val	Val
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	G1y	Lys	Leu
Lys 385	Pro	Thr	Met	Ala	Phe 390	Met	Ser	Gly	Lys	L'eu 395	Lys	Ile	Lys	Gly	Asn 400
Met	Ala	Leu	Ala	He	Lys	Leu	Glu	Lys	Leu	Met	Asn	Gln	Met	Asn	Ala

65 ·

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									66							
		115					120				125					
			cga Arg												4	132
			aaa Lys		-	_									4	180
_			cag Gln	-	_		_	_	-	-	-	_	_	•	5	528
-		-	atg Met 180	_	-			_				_		_	5	576
			tct Ser												6	524
taa *															6	527
	<2 <2	?10> ?11> ?12> ?13>	208	sap	oiens	;										

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				85					90					95		
Asn	Leu	Lys	Lys 100	Thr	Ala	Asp	Met	Asp 105		Gly	Gln	Ile	Gly 110	Phe	His	
Arg	Gln	Lys 115	Asp	Val	Lys	IJе	Val 120	Thr	Val	Glu	Lys	Lys 125	۷a٦	Asn	Glu	
Пe	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	Val ⁻	Glu	Arg 140	Phe	Pro	Asp	Leu	
Ala 145	Ala	Glu	Lys	Glu	Cys 150	Arg	Asp	Arg	Glu	Glu 155	Arg	Asn	Glu	Lys	Lys 160	
Ala	Gln	Ile	Gln	G1u 165	Met	Lys	Lys	Arg	G1u 170	Lys	Glu	Glu	Met	Lys 175	Lys	
			180					185			Ser		190			
G1u	Asn	Met 195	Ser	Ser	Asn	Gln	Asp 200	Gly	Asn	Asp	Ser	Asp 205	Glu	Phe	Met	
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		220>	٠													
		221> 222>		(4	174)											
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-4-		100>									,					40
											ctg Leu					48
											gtc Val					. 96
											nag Xaa					144
					_		-				999 Gly	_	_		-	192

68

50 55 60 ccc cag tgc ggc ttc agc aac gcc gtg gtg cag atc ctg cgg ctg cac 240 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 65 70 75 ggc gtc cgc gat tac gcg gcc tac aac gtg ctg gac gac ccg gag ctc 288 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 85 336 cga caa ggc att aaa gac tat tcc aac tgg ccc acc atc ccg caa gtg Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 100 105 110 tac ctc aat ggc gag ttt gta ggg ggc tgt gac att ctt ctg cag atg 384 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 115 120 125 cac cag aat ggg gac ttg gtg gaa gaa ctg aaa aag ctg ggg atc cac 432 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 130 135 tcc gcc ctt tta gat gaa aag aaa gac caa gac tcc aag tga 474 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys * 145 150 155. <210> 42 <211> 157 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(157) <223> Xaa = Any Amino Acid <400> 42 Met Ser Gly Ser Leu Gly Arg Ala Ala Ala Ala Leu Leu Arg Trp Arg 10 Leu Cys Ala Gly Gly Gly Leu Trp Gly Pro Val Val Arg Thr Ala 25 Gly Ser Ala Pro Gly Gly Gly Gly Ser Ala Xaa Xaa Leu Asp Ala Leu 45 35 40

Val Lys Lys Asp Lys Val Val Val Phe Leu Lys Gly Thr Pro Glu Gln 55 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 70 75 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 90 Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 105 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 120 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 135 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys 145 150 155 <210> 43 <211> 1032 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1032) <400> 43 48 Met Gly Gly Pro Arg Gly Ala Gly Trp Val Ala Ala Gly Leu Leu Leu 1 10 15 ggc gcg ggc gcc tgc tac tgc att tac agg ctg acc cgg ggt cgg cgg 96 Gly Ala Gly Ala Cys Tyr Cys Ile Tyr Arg Leu Thr Arg Gly Arg Arg 20 25 cgg ggc gac cgc gag ctc ggg ata cgc tct tcg aag tcc gca ggt qcc 144 Arg Gly Asp Arg Glu Leu Gly Ile Arg Ser Ser Lys Ser Ala Gly Ala 35 40 45 ctg gaa gaa ggg acg tca gag ggt cag ttg tgc ggg cgc tcg gcc cgg 192 Leu Glu Glu Gly Thr Ser Glu Gly Gln Leu Cys Gly Arg Ser Ala Arg 50 55 cct cag acg gga ggt acc tgg gag tca cag tgg tcc aag acc tcg cag 240 Pro Gln Thr Gly Gly Thr Trp Glu Ser Gln Trp Ser Lys Thr Ser Gln 65 70 75 80

	-	_							-	_			gct Ala 95	-		288
		_					-	_				-	cct Pro	_		336
		-	-	-	-			_			_	_	ttt Phe		,	384
-			-			_	_	_					gtt Val	_		432
							-						tta Leu			480
-				-	Ser			-	-			_	ata Ile 175	_		528
					-	-		-					ctg Leu			576
					-		-						act Thr			624
													ctg Leu			672
									-				ttg Leu			720
						_			-				ctt Leu 255			768

	gcc Ala			_								_	-		-	816
-	aag Lys					_	_		_						_	864
	tgc Cys 290				_				-		_					912
_	ggt Gly		_			_								_		960
	aga Arg													_	-	1008
-	aca Thr						tga *									1032
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Gly	Ala	Gly	A1 a 20	Cys	Tyr	Cys	Ile	Tyr 25	Arg	Leu	Thr	Arg	Gly 30	Arg	Arg	
Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40	Arg	Ser	Ser	Lys	Ser 45	Ala	Gly	Ala	
Leu	G1u 50		Gly	Thr	Ser	G1u 55		Gln	Leu	Cys	Gly 60		Ser	Ala	Arg	
Pro 65	Gln	Thr	Gly	Gly	Thr 70		Glu	Ser	Gln	Trp 75		Lys	Thr	Ser	G1n 80	
	Glu	Asp	Leu	Thr 85	_	Gly	Ser	Tyr	Asp 90		Val	Leu	Asn	A1a 95		

Gln Le	u Gln	Lys 100	Leu	Leu	Tyr	Leu	Leu 105	Glu	Ser	Thr	Glu	Asp 110	Pro	Val
Ile Il	e Glu 115	Arg	Ala	Leu	Ile	Thr 120	Leu	Gly	Asn	Asn	Ala 125	Ala	Phe	Ser
Val As 13		Ala	Пe	Ile	Arg 135	Glu	Leu	Gly	Gly	Ile 140	Pro	Ile	Val	Ala
Asn Ly 145	s Ile	Asn	His	Ser 150	Asn	G1n	Ser	He	Lys 155	Glu	Lys	Aìa	Leu	Asn 160
Ala Le			165					170				•	175	
Ile Ty		180			•		185				_	190		
Ser Al	195	•				200					205			
Thr As	0				215				Ť	220		·		
Gln Va 225				230					235					240
Leu Le			245					250				_	255	
Arg Al		260					265				·	270		
Ala Ly	275					280					285			
Asn Cy 29	0				295					300				
Glu Gl 305				310			,	_	315		-			320
Ile Ar			325	,		пі	ASP	330	GIU	Val	Lys	GIU	335	Val
Val Th	rite	340	PIO	Lys	116									
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73

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						_	-		_		-	_		ttt Phe 95	-	288
	_	_				_		-						aca Thr		336
	-		-	•	_			_	_		-		_	tgg Trp		384
	-							-				-		ctg Leu	_	432
_	_			-		-	_	_	-	-	-			caa Gln		480
gaa	tat	aag	ссс	ctt	tcg	ggc	att	cgg	tac	atg	tgg	tcg	tac	cat	tta	528

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Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu	
						agt Ser	•				-	•	_		_	576
		-		_		gnt Xaa		_				-	_			624
-			-			atc Ile 215		_								672
						gtg Val										720
		-	-			gtc Val	_		-			-	-		_	768
				_		agg Arg		_						-	-	816
		-		-		tac Tyr	-					-		-		864
			_			999 Gly 295		-		-			-		-	912
						aag Lys			-							960
						att Ile										1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

Phe Thr Val Phe Gly Gly Leu Met Ala Phe Asn Tyr Asn Arg Ala Phe 340 345 350	
cag gtg tgg gca gtc cct ctg tta ttg gta gct ttt ttt gcc tac tta Gln Val Trp Ala Val Pro Leu Leu Leu Val Ala Phe Phe Ala Tyr Leu 355 360 365	1104
gta gcc cat agt ttt tta tct gtg ttt gaa act gtg ctg gat gca ctt Val Ala His Ser Phe Leu Ser Val Phe Glu Thr Val Leu Asp Ala Leu 370 375 380	1152
ttc ctg tgt ttt gct gtt gat ctg gaa aca aat gat gga tcg tca gaa Phe Leu Cys Phe Ala Val Asp Leu Glu Thr Asn Asp Gly Ser Ser Glu 385 390 395 400	1200
aag ccc tac ttt atg gat caa gaa ttt ctg agt ttc gta aaa agg agc Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 410 415	1248
aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430	1296
aat gag gag gga aca gaa ctc cag gcc att gtg aga tag Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg * 435 440	1335
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Leu Ser Leu Ala Met Met Phe Thr Phe Arg Phe Ile Thr Thr Leu Leu 20 25 30	
Val His Ile Phe Ile Ser Leu Val Ile Leu Gly Leu Leu Phe Val Cys	

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Ile
G1u 65	Leu	Asp	Thr	Glu	Arg 70	Glu	Asn	Met	Lys	Cys 75	Val	Leu	Gly	Phe	Ala 80
Ile	Val	Ser	Thr	Gly 85	Ile	Thr	Ala	Val	Leu 90	Leu	Val	Leu	He	Phe 95	Val
Leu	Arg	Lys	Arg 100	Ile	Lys	Leu	Thr	Val. 105	Glu	Leu	Phe	Gln	Ile 110	Thr	Asn
Lys	Ala	Ile 115	Ser	Ser	Ala	Pro	Phe 120	Leu	Leu	Phe	Gln	Pro 125	Leu	Trp	Thr
Phe	Ala 130	Ile	Leu	Ile	Phe	Phe 135	Trp	Val	Leu	Trp	Val 140	Ala	Val	Leu	Leu
Ser 145	Leu	Gly	Thr	Ala	Gly 150	Ala	Ala	Gln	Val	Met 155	Glu	Gly	Gly	Gln	Val 160
Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Пe	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu
Ile	Gly	Leu	Ile 180	Trp	Thr	Ser	Glu	Phe 185	Ile	Leu	Ala	Cys	Gln 190	Gln	Met
	Ile	195					200					205			
Așp	Pro 210	Pro	Asp	His	Pro	Ile 215	Leu	Ser	Ser	Leu	Ser 220	Ile	Leu	Phe	Phe
225	His				230		-			235					240
	Ile			245					250					255	
G1n	His	Gly	A1a 260	Leu	Ser	Arg	Tyr	Leu 265	Phe	Arg	Cys	Cys	Tyr 270	Cys	Cys
	Trp	275		•	-	•	280					285			
	Thr 290					295				-	300			Ū	,
305	Phe				310					315					320
Cys	Phe	Gly	Asp	Phe 325	Пe	He	Phe	Leu	Gly 330	Lys	Val	Leu	Val	Va1 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Va1	Ala	Phe	Phe 365	Ala	Tyr	Leu
Val	Ala 370	His	Ser	Phe	Leu	Ser 375	Val	Phe	Glu	Thr	Val 380	Leu	Asp	Ala	Leu
Phe	Leu	Cvs	Phe	Ala	Val	Asn	Leu	Glu	Thr	Asn	Asn	Glv	Ser	Ser	Glu

385					390					395					400	
				405	·				410				Lys	415		
	-		420			_		425		·	-	His	Ser 430	Leu	Arg	
Asn	Glu	G1u 435	Gly	Thr	Glu	Leu	G1n 440	Ala	Ile	Val	Arg					
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		100>											•			
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													gga Gly 30		_	96
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													tta Leu	-		192
						-							aag Lys			240
	_							-				-	ctt Leu	_	-	288
							_	-		-			cag Gln			336

78

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				atg Met											96
	-	-		gaa Glu	-	_	-			-		-	-	1	.44
				gaa Glu 55										1	.92
				gtg Val	_				_	_	-	-	-	2	40
				gcc Ala										2	88
				acc Thr										3	36
				tgt Cys								_		3	84
			-	999 Gly 135	_	-	_	_						4	32
				ctt Leu										4	80
				tgg Trp					taa *					5	16

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<212> PRT

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<220>

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aag ttc aag ctt ttt acc ttg gtg tct gcc tgt atc cca gtg ttc agg
Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

-	-	-			aag Lys	_					-				gat Asp	144
_				_	aga Arg	_					-				•	192
		-			gag Glu 70	_					_	_	-	_		240
	-		-	_	ttc Phe		_	_	-		-	-			-	288
	_				gac Asp		_	-							_	336
	-				gtt Val	-		Glu		-	-	-		-		384
-					ctg Leu	-					-		-		_	432
		_		_	gca Ala 150	_	-	-		_	_	-	_		-	480
-				-	tgg Trp			_					-		ggt Gly	528
					ctg Leu											576
	-	_		_	tcc Ser	-			_		_			-		624

82

				cag Gln								-	-	_	672
				agc Ser 230							-		_	-	720
_	_	_	_	tgc Cys		-			_		_				768
	-			cac His	-	-				_	_			-	816
-				gaa G1u	-		-	_			_		_		864
ccg Pro	tga *														870

<210> 52

<211> 289

<212> PRT

<213> Homo sapiens

<400> 52

 Met
 Pro
 Leu
 Leu
 Lys
 Leu
 Val
 His
 Gly
 Ser
 Pro
 Leu
 Val
 Phe
 Gly
 Glu
 Gly
 Fro
 Val
 Phe
 Arg
 Arg
 Arg
 Arg
 Ser
 Phe
 Leu
 Lys
 Arg
 Leu
 Arg
 Arg
 Leu
 Phe
 Leu
 Lys
 Arg
 Leu
 Arg
 Arg</th

83

100 105 110 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro 120 Lys Gly Lys Lys Phe Leu Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys 140 130 135 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly Arg 150 155 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly 165 170 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys 180 185 190 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 200 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 230 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His 275 280 285 Pro <210> 53 <211> 1041 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1041) <221> misc feature <222> (1)...(1041) <223> n = A.T.C or G<400> 53 48 Met Pro Arg Val Phe Val Phe Arg Ala Leu Leu Val Leu Ile Phe

10

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		_				-					tat Tyr					· 144
	-	_							-	-	atc Ile 60		-	_		192
		_	-	-		_		_	_	_	gtg Val	_	-			240
											ctg Leu					288
											gat Asp					336
						_				-	gca Ala	_	_		_	384
-		-					_	-			agt Ser 140					432
	_			_	_		-	_	-	_	cgg Arg					480
											cat His					528
											gaa Glu					576

				gct Ala			_	-		-			624
				gcc Ala 215	-						_	-	672
				ctg Leu	-				-	_		cac His 240	720
			_	cag G1n		_	-		_				768
	_	-		cta Leu	_				_				816
				cgc Arg									864
				aat Asn 295				_				_	912
				agc Ser						_			960
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<212> PRT

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Ser	Asp 290	Glu	Ala	Val	Thr	Asn 295	Gly	Leu	Arg	Asp	Gly 300	Ile	Val	Phe	Val	
Leu 305	Lys	Cys	Leu	Asp	Phe 310	Ser	Leu	Val	Val	Asn 315	Val	Lys	Lys	Ile	Pro 320	,
Phe	Ile	Ile	Leu	Ser 325	Glu	Glu	Phe	Ile	Asp 330	Pro	Lys	Ser	His	Lys 335	Phe	
Val	Leu	Arg	Leu 340	Gln	Ser	Glu	Thr	Ser 345	Val							
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		212>														
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		220> 221>	cnc													
				(1	195)											
	_/	100>	55													
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														Thr 15		
gtg	gcc	ggc	agc	ССС	cga	ggc	cat	999	cag	agc	cgc	gag	aca	acc	cag	96
Val	Ala	Gly	Ser 20	Pro	Arg	Gly	His	G1y 25	Gln	Ser	Arg	G1u	Thr 30	Thr	Gln	
														cac		144
ษาน	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Inr	Arg	45	Asn	His	Asn	
														cca		192
Arg	Arg 50	Thr	Met	Ala	Asp	Arg 55	Lys	Arg	Ser	Lys	Gly 60	Met	Ile	Pro	Ser	
tga																195

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<213> Homo sapiens

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Glu	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Thr	Arg	Ala 45	Asn	His	Asn	
Arg	Arg 50	Thr	Met	Ala	Asp	Arg 55	Lys	Arg	Ser	Lys	Gly [.] 60	Met	Ile	Pro	Ser	
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													Val			40
													gag Glu 30		-	96
													cac His			144
													gaa Glu			192
													ctg Leu			240
										-			ctc Leu		-	288

	tgg Trp									_						336
	cta Leu					_			-	_		-		_		384
	cga Arg 130	_		-					_					-	_	432
	aag Lys			_						-		-				480
-	ggc Gly		_	_	-	_										528
	aag Lys				-	-	_	_	-							576
	tat Tyr						-	-	-		-		-	-	-	624
	gca Ala 210															672
	cct Pro															720
_	atc Ile			_	_	-	-							_		768
agg Arg	ctg Leu								-							816

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-			_	_		-	-		-		 aag Lys	_	864
					_						gtc Val	_	912
		_	_	-			_	-	-	-	 cag Gln		960
-			_	-						-	 ctg Leu 335	-	1008
tag *													1011

90

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<210> 58

<211> 336

<212> PRT

<213> Homo sapiens

<400> 58

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Arg Pro Ser Gly Gly Ala Ala Gly Glu Arg Glu Leu Asp Glu Val Asp 25

Met Ser Asp Leu Ser Pro Glu Glu Gln Trp Arg Val Glu His Ala Arg

Met His Ala Lys His Arg Gly His Glu Ala Met His Ala Glu Met Val 55

Leu Ile Leu Ile Ala Thr Leu Val Val Ala Gln Leu Leu Leu Val Gln 70 75

Trp Lys Gln Arg His Pro Arg Ser Tyr Asn Met Val Thr Leu Phe Gln

Met Trp Val Val Pro Leu Tyr Phe Thr Val Lys Leu His Trp Trp Arg 100 105

Phe Leu Val Ile Trp Ile Leu Phe Ser Ala Val Thr Ala Phe Val Thr 115 125 120

91

Phe Arg Ala Thr Arg Lys Pro Leu Val Gln Thr Thr Pro Arg Leu Val 135 140 130 Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile 150 155 Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu 170 165 Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu 185 180 Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met 200 Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln 230 235 Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr 245 250 255 Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp 260 265 Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val 280 Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met 295 300 Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro 310 315 Val Ile Ile Gly Val Val Gln Gly Ile Asn Tyr Ile Leu Gly Leu Glu 325 330 <210> 59 <211> 393 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(393) <221> misc feature <222> (1)...(393) <223> n = A,T,C or G<400> 59 48 atg ctg gac ttg cag aag cag ctg ggc aga tnc cag ggn gcc ana ttt Met Leu Asp Leu Gln Lys Gln Leu Gly Arg Xaa Gln Xaa Ala Xaa Phe

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15

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 -				cct Pro	-								192
 -			-	agt Ser 70			-						240
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	-		-	ctg Leu			_	-					336
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			_	_				-		tta Leu 75			-	_			240
								-		caa G1n			-			·	288
		-		-		-	_		-	caa Gln	_						336
_		-			-					cca Pro	_			-	-		384
					_			_		att Ile		-	-				432
		-		_			-		_	aaa Lys 155					-		480
	-						_	_		999 Gly							528
_								-		gga Gly		-			-		576
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tat Tyr							-	-							-	816
aat Asn	-	-		_			_	_						_		864
tgt Cys																912
tgg Trp 305					_		-						-		-	960
gcg Ala			_		_		-				_			_		1008
tcc Ser			Пe	Leu		Glu			Pro					_		1056
gtg Val					-		-	-		-		_	_			1104
aac Asn l																1152
ttg (_						_		_		1200

96

385 390 395 400 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 405 410 415 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc 1296 Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 420 425 430 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa 1383 Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu * 450 455 460 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 10 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu 40 Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro 55 Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 70 -75 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 100 105 110

Cys	Glu	Asp 115	Arg	Pro	Lys	His	Lys 120	Thr	Arg	Pro	Ser	His 125	Ser	Glu	۷a۱
Trp	Gly 130	Tyr	Gly	Phe	Leu	Ser 135	Val	Thr	IJе	Ile	Asn 140	Leu	Ala	Ser	Leu
Leu 145	Gly	Leu	Ile	Leu	Thr 150	Pro	Leu	IJе	Lys	Lys 155	Ser	Tyr	Phe	Pro	Lys 160
				165		Gly			170					175	
Ala	Ile	Phe	Gln 180	Leu	Ile	Pro	Glu	Ala 185	Phe	Gly	Phe	Asp	Pro 190	Lys	Val
·	•	195			-	Ala	200				·	205		•	
	210				Ť	Met 215		-			220				Ī
225					230	Phe	-		·	235					240
-				245	•	Ala			250					255	-
·			260			Thr		265					270		·
		275				Leu	280					285			
	290				-	Pro 295	-				300				
305					310	Asp				315			-		320
		-		325		Thr			330					335	
			340		•	Glu		345					350	·	
		355				Gly	360			_		365			
	370					Ser 375	•	•		·	380			·	
385					390	Ala				395					400
				405		Ser			410					415	
·			420		-	Val		425		•		•	430		
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				gag Glu 70								-		240
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	ctc Leu 50														-	192
	aaa Lys		-	-						_	-			_		240
	tcc Ser													_	_	288
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	aca Thr		-	-			-			-				_		384
_	ctg Leu 130	-					_	-			_		-		•	432
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	San	Lou	Dho		C1 2	۸٦٠	Cuc	Dha		The	۸٦٠	110	Acn		Lou	

Val Ser Leu Phe Leu Gln Ala Cys Phe Leu Thr Ala Ile Asn Tyr Leu

25

30

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Ser	Leu 50		Val	Pro	Arg	Pro 55		Pro	Gly	His	His 60		Pro	Pro	Ala	
Va1 65	Lys	Glu	Met	Lys	G1u 70	Thr	Gln	Thr	G1u	Arg 75	Asp	Ile	Pro	Met	Ser 80	
	Ser			85		•			90					95	·	
	Ser	•	100					105					110		·	
	Thr	115					120					125		·		
	Leu 130	•				135					140					
145	Pro				150				·	155		Val	Asn	Pro	A1a 160	
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Met 1 caa	<td>222> 100> gca Ala</td> <td>(1) 67 gag Glu tgc</td> <td>gct Ala 5 ctg</td> <td>ggg Gly ctg</td> <td>Asp</td> <td>Leu gag</td> <td>Ser agg</td> <td>Thr 10 gct</td> <td>Ala tca</td> <td>Leu</td> <td>Glu tac</td> <td>Arg aac</td> <td>Phe 15 aac</td> <td>Gly cgt</td> <td></td>	222> 100> gca Ala	(1) 67 gag Glu tgc	gct Ala 5 ctg	ggg Gly ctg	Asp	Leu gag	Ser agg	Thr 10 gct	Ala tca	Leu	Glu tac	Arg aac	Phe 15 aac	Gly cgt	
Met 1 caa Gln gcc	caa Gln gcc Ala	222> 400> gca Ala atc Ile	(1) 67 gag Glu tgc Cys 20 cgg	gct Ala 5 ctg Leu	ggg Gly ctg Leu	Asp cct Pro	gag Glu gga	agg Arg 25 gac	Thr 10 gct Ala gtg	Ala tca Ser	gcc Ala	Glu tac Tyr	aac Asn 30	Phe 15 aac Asn	cgt Arg	
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Met 1 caa Gln gcc Ala	caa Gln gcc Ala	222> 100> gca Ala atc Ile gcc Ala 35 cgc	(1) 67 gag Glu tgc Cys 20 cgg Arg	gct Ala 5 ctg Leu cga Arg	ggg Gly ctg Leu ctc Leu	Asp cct Pro cag Gln	gag Glu gga Gly 40	ser agg Arg 25 gac Asp	Thr 10 gct Ala gtg Val	tca Ser gca Ala	gcc Ala ggc Gly	tac Tyr gcc Ala 45	aac Asn 30 ctg Leu	Phe 15 aac Asn gag Glu gcc	cgt Arg gat Asp	96

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	gac Asp															288
	gcg Ala		-	_	•		_					-		_	_	336
	cgc Arg		-		-	-									_	384
-	cgc Arg 130	tga *														393
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Ala	G]n	A1a 35		Arg	Leu	Gln	Gly 40		Val	Ala	Gly	Ala 45		G1u	Asp	
Leu	Glu 50		Ala	۷al	Glu	Leu 55		Gly	Gly	Arg	Gly 60		Ala	Ala	Arg	
G1n 65	Ser	Phe	Val	Gln	Arg 70		Leu	Leu	Ala	Arg 75	Leu	Gln	Gly	Arg	Asp 80	
	Asp	Ala	Arg	Arg		Phe	G1u	Arg			Arg	Leu	Gly			
				ጸፍ					QΛ					95		
Phe	Ala	Arg	Arg 100	85 G1n	Leu	Val	Leu	Leu 105	90 Asn	Pro	Tyr	Ala	Ala 110	95 Leu	Cys	

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	_		_	_	cag Gln	_									144
				_	tgc Cys	-		_	-					_	192
		_	-	_	ggc Gly 70			_							240
	_	-			tct Ser				-	-				-	288
					atg Met										336
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104

PCT/US00/29052

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	Lys	Val	Va1 35	Ser	Gly	Arg	Ile	Ile 40	Asn	Gly	Tyr	Cys	Arg 45	-	Asp	Trp	
						tac Tyr									-	-	192
						ctg Leu 70											240
						agc Ser											288
						gtg Val			-		-				-		336
						gcc Ala											384
						gcc Ala								-	-		432
						ata Ile 150											480
						gcc Ala											528
						gct Ala					-					_	576
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,	aag	acc	cag	ggc	ссс	agc	acg	ggg	ctg	gac	tga						657

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Leu Leu Ser Phe Val Tyr Arg Thr Ser Ser Val Gln Leu His Val Ala
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                                            60
Gly Leu Gln Pro Val Leu Leu Gln Asp Arg Arg Val Glu Asn Val Asp
Leu Thr Ser Val Val Ser Gly His Leu Asp Tyr Ala Lys Gln Met Asp
                                    90
Ala Ile Leu Lys Ala Val Gly Ile Arg Thr Lys Pro Gly Trp Asp Glu
                                105
Lys Gly Leu Leu Ala Pro Gly Cys Leu Pro Ser Glu Glu Pro Arg
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Gln Ala Ala Ala Ala Ser Ser Gly Glu Thr Pro His Gln Val Gly
                       135
Gln Thr Gln Gly Pro Ile Ser Gly Asp Thr Ser Lys Leu Ala Met Ser
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                                        155
Thr Asp Pro Ser Gln Ala Gln Val Pro Val Gly Leu Asp Gln Ser Glu
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Gly Ala Ser Leu Pro Ala Ala Ala Ser Pro Glu Arg Pro Pro Ile Cys
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	gat Asp											_			240
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_	tca Ser	-	_	-				-	-		_		-	•	336
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Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
                    70
                                        75
Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
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Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
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                                105
                                                    110
Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
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                                     10
                                                          15
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	cct Pro 50			_						_					_	192
	ctt Leu				-	-			-				-	_	_	240
	aat Asn			-			-			_			-			288
	gtg Val			Leu												336
	cag G1n	tga *														345
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-	ggg Gly 130				_	_					_		_		_	432
	aat Asn	-		-	-	•	_	-		-	_	-	•		-	480
_	aca Thr			-				_		_			-			528
	gac Asp				-							_	-	_	_	576
	atg Met	-		-		_			_					~	~ ~	624
	ttc Phe 210		-		_							-	_	_	_	672
	ctt Leu				-							-		-	-	720
-	atg Met		-		_		-		-	-		-				768
	gag G1u			-											_	816
_	gtg Val				-	_		-	-			-	-			864

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Leu	Ala	Arg 35	Arg	Arg	Lys	Lys	11e 40	Leu	Phe	Tyr	Cys	His 45	Phe	Pro	Asp	
Leu	Leu 50	Leu	Thr	Lys	Arg	Asp 55	Ser	Phe	Leu	Lys	Arg 60	Leu	Tyr	Arg	Ala	
Pro 65	Ile	Asp	Trp	Пe	G1u 70	Glu	Tyr	Thr	Thr	G1y 75	Met	Ala	Asp	Cys	Ile 80	
Leu	Val	Asn	Ser	G1n 85	Phe	Thr	Ala ·	Ala	Val 90	Phe	Lys	Glu	Thr	Phe 95	Lys	
Ser	Leu	Ser	His 100	Ile	Asp	Pro	Asp	Val 105	Leu	Tyr	Pro	Ser	Leu 110	Asn	Val	
Thr	Ser	Phe 115	Asp	Ser	Val	Val	Pro 120	Glu	Lys	Leu	Asp	Asp 125	Leu	Val	Pro	
Lys	Gly 130	Lys	Lys	Phe	Leu	Leu 135	Leu	Ser	Ile	Asn	Arg 140	Tyr	G1u	Arg	Lys	
Lys 145	Asn	Leu	Thr	Leu	Ala 150	Leu	Glu	Ala	Leu	Val 155	Gln	Leu	Arg	Gly	Arg 160	
Leu	Thr	Ser	Gln	Asp 165	Trp	Glu	Arg	Val	His 170	Leu	Пe	Val	Ala	Gly 175	Gly	
Tyr	Asp	Glu	Arg 180	Val	Leu	Glu	Asn	Val 185	Glu	His	Tyr	Gln	G1u 190	Leu	Lys	

113

Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 195 200 205 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 235 230 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 245 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Arg Glu Pro Ser 280 Leu Lys Ala Thr Met Gly Leu Ala Gly Arg Ala Arg Val Lys Glu Lys 295 300 Phe Ser Pro Glu Ala Phe Thr Glu Gln Leu Tyr Arg Tyr Val Thr Lys 305 310 315 320 Leu Leu Val

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_			-	-	gcc Ala			-			-			_	_	. 19	2
	-				ata Ile 70	-		-	_	_		-	_	_	-	24	.0
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					ctg Leu											57	6
			-		aca Thr		_		-							62	4

115

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Gly Val Gly Glu Leu Ile Val Arg Glu Leu Asp Leu Ala Ser Leu Arg
Ser Val Arg Ala Phe Cys Gln Glu Met Leu Gln Glu Glu Pro Arg Leu
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Asp Val Leu Ile Asn Asn Ala Gly Ile Phe Gln Cys Pro Tyr Met Lys
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                                                    110
Thr Glu Asp Gly Phe Glu Met Gln Phe Gly Val Asn His Leu Gly His
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Phe Leu Leu Thr Asn Leu Leu Leu Gly Leu Leu Lys Ser Ser Ala Pro
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Ser Arg Ile Val Val Val Ser Ser Lys Leu Tyr Lys Tyr Gly Asp Ile
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Asn Phe Asp Asp Leu Asn Ser Glu Gln Ser Tyr Asn Lys Ser Phe Cys
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Tyr Ser Arg Ser Lys Leu Ala Asn Ile Leu Phe Thr Arg Glu Leu Ala
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Arg Arg Leu Glu Gly Thr Asn Val Thr Val Asn Val Leu His Pro Gly
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Ile Val Arg Thr Asn Leu Gly Arg His Ile His Ile Pro Leu Leu Val
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Glu Gly Ala Gln Thr Ser Ile Tyr Leu Ala Ser Ser Pro Glu Val Glu
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Gly Val Ser Gly Arg Tyr Phe Gly Asp Cys Lys Glu Glu Glu Leu Leu
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-	al I		-			_									ctt Leu		672
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_		_	_	-		-	-	-	-	-	-	-			tgg Trp		816
		er	-			-									aag Lys		864
	r A				-										tta Leu		912
	n Ā			•				•		-		-			gtt Val		960
_						-	-				-				tcc Ser 335		1008
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Cā	a t	tc	aat	gct	cat	atc	tgg	acc	aaa	tca	aaa	ttc	ctt	ggg	atg	tca	1104

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	aaa Lys				-	-										1	.296
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	aag Lys 450				_			-		-					_	1	.392
	gca Ala															1	.440
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	aga Arg							-								1	.584
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	tta Leu										tag *					1716
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Cys 65	Lys	Ser	Glu	Gln	Arg 70		Ser	Ser	Leu	Pro 75		Gly	Pro	Val	Leu 80	
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Gly	His	Ser	Pro 100		Ser	Ser	Ser	Leu 105		Ser	Pro	Ser	His 110		Asn	
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Ser	Gly	Asn	Ser	Leu 165	Lys	Arg	Pro	Asp	Thr 170	Thr	Glu	Ser	Leu	Asn 175	Ser	
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Asp	Arg	Asp 195		Asp	Ala	Glu	A1 a 200		Ser	Val	Glu	G1u 205		Lys	Ser	

Val	Ile 210	Met	His	Leu	Leu	Ser 215	Gln	Val	Arg	Leu	Gly 220	Met	Asp	Leu	Thi
Lys 225	Val	Val	Leu	Pro	Thr 230	Phe	Ile	Leu	Glu	Arg 235	Arg	Ser	Leu	Leu	G1u 240
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Tyr	Asn 290	Pro	IJе	Leu	Gly	G1u 295	Пe	Phe	Gln	Cys	His 300	Trp	Thr	Leu	Pro
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Trp	Val	Ser	Lys	Asn 325	Ser	Val	Thr	Phe	Val 330	Ala	Glu	Gln	Val	Ser 335	His
His	Pro	Pro	Ile 340	Ser	Ala	Phe	Tyr	A1a 345	Glu	Cys	Phe	Asn	Lys 350	Lys	Πe
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Ser	Lys	Thr	G1y 420	Tyr	Ser	Ala	Asn	Ile 425	Ile	Phe	His	Thr	Lys 430	Pro	Phe
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Asp	Lys 450	Lys	Ser	Phe	Cys	Ser 455	He	Glu	Gly	Glu	Trp 460	Asn	Gly	Val	Met
Tyr 465	Ala	Lys	Tyr	Ala	Thr 470	Gly	Glu	Asn	Thr	Va1 475		Val	Asp	Thr	Lys 480
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Ala Gly Leu Pro Ser Ser Arg Ser Phe Met Gly Phe Ala Ala Pro Phe
35
40
45

acc aac aag cga aag gct tac tcg gag cgt aga atc atg ggg tac tca

Thr Asn Lys Arg Lys Ala Tyr Ser Glu Arg Arg Ile Met Gly Tyr Ser

50 55 60

atg cag gag atg tat gag gtg gtg tcc aac gtc cag gag tat cgt gag
Met Gln Glu Met Tyr Glu Val Val Ser Asn Val Gln Glu Tyr Arg Glu
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ttt gtg ccc tgg tgt aag aag tct ctg gtg gta tcc agc cgt aag ggt
Phe Val Pro Trp Cys Lys Lys Ser Leu Val Val Ser Ser Arg Lys Gly
85 90 95

cat ttg aaa gcc cag ctg gag gtt ggc ttt cca cct gtc atg gaa cgt
His Leu Lys Ala Gln Leu Glu Val Gly Phe Pro Pro Val Met Glu Arg
100 105 110

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Tyr Thr Ser Ala Val Ser Met Val Lys Pro His Met Val Lys Ala Val
115 120 125

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														ttt Phe	-	480
			_		_		_	_			-	_	-	acc Thr 175	•	528
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Thr	Asn 50		Arg	Lys	Ala	Tyr 55		Glu	Arg	Arg	Ile 60		Gly	Tyr	Ser	
Met 65		Glu	Met	Tyr	Glu 70		Val	Ser	Asn	Va1 75		Glu	Tyr	Arg	G1u 80	
	Val	Pro		Cys 85		Lys	Ser	Leu	Va1 90		Ser	Ser	Arg	Lys 95		

124

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	gtc Val	_	-	-				-	_		_	_				336
	gtc Val		-	-	-		-									384
	att Ile 130		-		_					-			•		•	432
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	ctg Leu			_			_			-		_		-	•	528
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	Leu			165			·		170					175		
	Phe		180					185				Glu	Thr 190	Ala	Ile	
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127

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			-			tgt Cys				-			_				288
						ctg Leu		-	-	-				-			336
-		-		-		aaa Lys	-	_		-	-	•	_	•			384
		-			_	atc Ile 135	•	_	-	-	_				-		432
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Ala	Thr	Leu 35	Lys	Thr	Пe	Arg	Asn 40	Gly	Val	His	Lys	Ile 45	Asp	Thr	Tyr	
Leu	Asn 50	Ala	Ala	Leu	Asp	Leu 55	Leu	Gly	Gly	Glu	Asp 60	Gly	Leu	Cys	Gln	
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Pro	Ser	Pro	Pro	Asn 85	Gly	Cys	Gly	Ser	Pro 90	Leu	Phe	Gly	Val	His 95	Leu	
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Cys	Tyr	G1u 115	Thr	Cys	Gly	Lys	Ser 120	Lys	Asn	Asp	Cys	Asp 125	Glu	Glu	Phe	
Gln	Tyr 130	Cys	Leu	Ser	Lys	Ile 135	Cys	Arg	Asp	Val	Gln 140	Lys	Thr	Leu	Gly	
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														cgg Arg	_		432
					_				-				-	atc Ile		•	480
														gtc Val 175			528
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	٠	195				Ser	200					205			-		
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                                     10 .
                                                          15
ccc gag cgc tgg gga cct ggc cgc ttt gac tac tgg ggc aac tcc cac
                                                                       96
Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
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                                 25
cag atc atg cac ctg ctg agc gtg ggc tcc atc ctg cag ctg cac gcc
                                                                      144
Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
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PCT/US00/29052

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Gly Val Val Pro Asp Leu Leu Trp Ala Ala His His Ala Cys Pro Arg
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agg cac agc cta ttg tct cct ttg ctc agt gtg aca tca ttc aga cgc
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Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr Ser Phe Arg Arg
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                                 25
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	-							-			-			gcc Ala		384
-			-		-	-	_	-	_	_	-	-		gct Ala		432
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			att		ctt	_			-		-		-	-		288

				85					90					95		
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C	۸۰۰	Acn		Asn	110	Tun	Tun		۸٦ -	Thn	G1	۸15		Dno	۸٦ -	

	0.3	115	Di.	0.1		0.7	120	14-4	A7 -	1	1	125	A	Di	A7 -	
Pro	130	116	rne	GIU	Asn	G1u 135	vai	met	Ala	Leu	140	Arg	ASP	rne	АТА	
Lys 145	Asn	Lys	Asn	Lys	Glu 150	Gln	Arg	Leu	Arg	Ala 155	Pro	Asp	Leu	Glu	Tyr 160	
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							ccc Pro									432
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tca Ser	gta Val		tga *													492
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141

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170

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_		-	_		-		_		_		-		_	ttc Phe		480
					-	-	-							gcg Ala 175		528
		-					-	_						gtg Val	-	576
_							_			_				tcc Ser		624
														cag Gln		672
														cag Gln		720

	cag Gln	_		_				_	-		_			768
	gtg Val													816
-	gac Asp	• .	_	-	_	_	_		 _	-	-			864
_	cac His 290				-		-					-		912
	ctc Leu	_	-	-	_	_	_	-						960
	gac Asp	_		_		-		 -					_	1008
	ggt Gly	_		_				-						1056
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WO 01/29221

Gln	His 290	Gln	Val	Trp	Asp	Val 295	Ala	Phe	Glu	Glu	Thr 300	Gln	Gly	Leu	Trp	
Va1 305	Leu	Gln	Asp	Cys	Gln 310		Ala	Pro	Leu	Val 315		Tyr	Arg	Pro	Val 320	
	Asp	Gln	Trp	G1n 325		Val	Pro	Glu	Ser	Thr	Val	Leu	Lys	Lys 335		
Ser	Gly	Val	Leu 340		Gly	Asn	Trp	A1a 345		Leu	Glu	Gly	Ser 350		Gly	
Ala	Asp	A1a 355	Ser	Phe	Ser	Ser	Leu 360	Tyr	Lys	Ala	Thr	Phe 365	Asp	Asn	Val	
Thr	Ser 370		Leu	Lys	Lys	Lys 375	Glu	Glu	Arg	Leu	G1n 380	Gln	Gln	Leu	Glu	
Lys 385	Lys	Gln	Arg	Arg	Arg 390	Ser	Pro	Pro	Pro	G1y 395	Pro	Asp	Gly	His	Ala 400	
Lys	Lys	Met	Arg	Pro 405	Gly	Glu	Ala	Thr	Leu 410	Ser	Cys					
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Met 1 tta	<2 <2 <4 agt	221> 222> 400> gat Asp	(1). 105 ttg Leu	gaa Glu 5 cag	ġat Asp gaa	Asp	Glu tat	Thr gct	Pro 10 gag	Gln caa	Leu aag	Ser caa	Ala caa	His 15 att	Ala gag	48 96
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G1n 65	Glu	Ala	Пe	Ala	A1a 70	Val	Gly	Glu	Gly	Gly 75	Arg	Ile	Ala	Cys	Val 80	
														gaa Glu 95		288
	_					-								tat Tyr	gga Gly	336
														ccc Pro		384
														ccc Pro		432
	_		-	_		•			_	-		_	_	tac Tyr	_	480
-			_		-	-	-							gaa Glu 175		528
_	_	-					-	-	-	_		-		aga Arg		576
			-	-										gat Asp		624
	ctg Leu 210				atc Ile	tga *										645

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<213> Homo sapiens

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Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp
Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
                                             60
                        55
Gln Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
                    70
                                        75
Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
                85
                                    90
Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
                                105
Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
                            120
Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
                        135
Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
145
                    150
                                        155
Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
                165
                                    170
Ala Ala Glu Leu Leu Gly Val Lys Met Cys Thr Phe Val Pro Arg His
                                185
Thr Arg Asn Leu Ala Asn Glu Phe Arg Cys Tyr Val Asn Tyr Asp Ser
        195
                            200
                                                 205
Gly Leu Asp Cys Gly Ile
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Met Lys Ser Ser Thr Leu Leu Thr Ile Leu Val Leu Gln Ala Leu Leu
 1
                                     10
                                                          15
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151

	tct Ser												_	-	-	96	
	tgc Cys					_							-	-	-	144	
	ctc Leu 50					_		_			_	_		-		192	
	gac Asp															240	
	tgc Cys		-	_			tag *	,								264	
	<'a	210> 211> 212> 213>	87	o sap	oiens	5											
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Val	Ser	Thr	Ala 20	Val	Pro	Lys	Gly	Pro 25	Ala	Gly	Pro	Lys	Lys 30	Gln	Cys		
Trp	Cys	G1 <i>y</i> 35		Cys	Thr		Trp 40		Gly	Val	Trp	Thr 45		Asp	Asp		
Leu	Leu 50		Lys	Cys	Ala	Ala 55	Thr	Cys	Lys	Asn	Cys 60	Val	Pro	Val	Ser		
Thr 65	Asp	Lys	Gly _.	Ala	Thr 70		Tyr	Arg	Cys	Arg 75		Phe	Leu	Pro	Glu 80		
	Cys	Gly	Cys	Lys 85		His				, 3							
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												gaa Glu	96
-									-		-	gcc Ala	144
				-	_	_	-			-	-	atg Met	192
												acg Thr	240
												tcg Ser 95	288
												caa Gln	336
				gaa Glu		-		-			tag *		378

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<211> 125

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<213> Homo sapiens

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Val	Glu	Ser	Ile 20	Cys	Ser	Asn	Asn	Phe 25	Asp _.	Ser	Phe	Leu	His 30	Glu	Thr		
His	Glu	Asn 35		Tyr	Gly	Lys	Gly 40		Tyr	Phe	Ala	Lys 45		Ala	Ile		
Tyr	Ser 50	His	Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60	Val	Val	Met	Phe		
Va1 65	Ala	Gln	Val	Leu	Va1 70	Gly	Lys	Phe	Thr	G1u 75	Gly	Asn	Ile	Thr	Tyr 80		
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	Val	Asp	Thr	Arg	Ser 95	Asn		
Pro	Ser	Val	Phe 100	Val	He	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110	Gln	Tyr		
Val	Ile	Glu 115	Tyr	Thr	Glu	Asp	Lys 120	Ala	Cys	Val	Пe	Ser 125					
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_	_							_				-		gcc Ala			96
		_				_	-				_			aat Asn	-	-	144
														act Thr		1	192

							gaa Glu								240
-	 	_					ttt Phe				-		-	~ ~	288
							att Ile 105				_	_	_	_	336
				_	-		aaa Lys					-			384
	-		_				aca Thr						-		432
						-	caa Gln		_			-			480
		_	-	_	-	-	tca Ser	-			-	-		_	528
							tat Tyr 185								576
		-	_		_	-	caa Gln	-							624
							ttg Leu			-				-	672
				-	_		ctt Leu	_				_	-	-	720

				-		aac Asn			_						-	768
			_	-	_	tca Ser		-		_	-	_		•	•	816
		-	_	-	-	gaa G1u	-			-	-	•	_	•		864
					-	tat Tyr 295							_	-		912
						gag Glu					,				_	960
-	-	-			_	gct Ala	_		•		-			_		1008
-			-	-		tct Ser				-			_		-	1056
-		_	_	-	-	tgt Cys	_	-					-			1104
						tat Tyr 375										1152
-	-				-	tat Tyr		_			-				-	1200
						gaa Glu										1248

		_	_			_		-	tca Ser	_		_		-	1296
		_							gtť Val				Ser		1344
					_				aga Arg					 -	1392
	_	-	-	_		_	-		cta Leu	_	-		-	_	1440
			-	-			-		tct Ser 490		-			-	1488
					_	-		-	cga Arg	_					1536
									tgg Trp						1584
_		-	-		-				gta Val						1632
									aag Lys						1680
									aga Arg 570						1728
_								-	cga Arg						1776

157

				-		agt Ser				-				1	.824
_		-	-		-	gaa Glu 615	-	-	-	-	 -		-	1	.872
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						ata Ile						tga *		1	965
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Val	Ala	Glu		Cys	Gln	Asn	Thr		Glu	Thr	Phe	Leu	Glu	Ala	Ser
			20					25					30		
Lys	Leu	Leu	Leu	Thr	Tyr	Ala	Asp	Asn	Пe	Leu	Arg	Asn	Pro	Asn	Asp
		35			•		40					45			
Glu	Lys	Tyr	Arg	Ser	He	Arg	He	Gly	Asn	Thr	Ala	Phe	Ser	Thr	Arg
	50					55					60				
Leu	Leu	Pro	Val	Arg	Gly	Ala	Val	Glu	Cys	Leu	Phe	Glu	Met	Gly	Phe
65				•	70					75				•	80 1
Glu	Glu	Gly	Glu	Thr	His	Leu	Ile	Phe	Pro	Lys	Lys	Ala	Ser	Val	Glu
		•		85					90 -	·	•			95	
Gln	Leu	Gln	Lys	He	Arg	Asp	Leu	Ile	Ala	He	Glu	Arq	Ser	Ser	Arg
			100			•		105					110		
Leu	Asp	Glv		Asn	Lvs	Ser	His		Va1	Lvs	Ser	Ser	Gln	Gln	Pro
	F	115			_, -		120	-		-J -		125			
Δla	Δla		Thr	Gln	Leu	Pro				Ser	Ser		Pro	Ser	Glv
,,,,	130	50.		um	LCu	135		****	110	501	140	7.5.1		501	u.,
1		C1	114.	Th	A		A	01	61	61		C	۸	D	D
	ASTI	um	HIS	ınr	_	ASI	arg	GIN	uly		ser.	ser.	Asp	Pro	
145					150					155					160

Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	He	Leu	Glu	Val	Leu 175	Gln
Ser	Asn	IÌе	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu
Lys	Ala	Leu 195	Ala	Cys	Ile	Pro	Val 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Ile	Asn	Ile	Ser
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys		G1u 240
Phe	Phe	His	Trp	Val 245	Asn	Asn	۷a٦	Leu	Cys 250		Lys	Cys	Gly	Gly 255	Gln
Thr	Arg	Ser	Arg 260	Asp	Arg	Ser	Leu	Leu 265	Pro	Ser	Asp	Asp	G1u 270	Leu	Lys
·	-	275	-		Val		280		-		•	285			
	290				Arg	295					300				
305		-	•	•	Gly 310		•			315					320
				325	Glu				330	,	·	-		335	
	·		340		Tyr			345				•	350		-
,		355		•	Val	•	360					365			•
Trp	G1y 370	Lys	Lys	Leu	Ser	Tyr 375	Val	Ile	Ala	Phe	Ser 380	Lys	Asp	Glu	Val
Va1 385	Asp	Val	Thr	Trp	Arg 390	Tyr	Ser	Cys	Lys	His 395	Glu	Głu	Val	Ile	Ala 400
Arg	Arg	Thr	Lys	Va1 405	Lys	Glu	Ala	Leu	Leu 410	Arg	Asp	Thr	Ile	Asn 415	Gly
Leu	Asn	Lys	G1n 420	Arg	Gln	Leu	Phe	Leu 425	Ser	Glu	Asn	Arg	Arg 430	Lys	Glu
Leu	Leu	G1n 435	Arg	Ile	Ile	Val	G1u 440	Leu	Val	Glu	Phe	I1e 445	Ser	Pro	Lys
Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	Ile	Ser 460	Gly	Ser	Val	Ala
Trp 465	Arg	Val	Ala	Arg	Gly 470	Glu	Met	Gly	Leu	G1n 475	Arg	Lys	Glu	Thr	Leu 480
Phe	Пe	Pro	Cys	G1u 485	Asn	Glu	Lys	Ile	Ser 490	Lys	Gln	Leu	Ӊis	Leu 495	Cys
Tyr	Asn	Ile	Val 500	Lys	Asp	Arg	Tyr	Val 505	Arg	Val	Ser	Asn	Asn 510	Asn	Gln

Thr	Ile	Ser 515	Gly	Trp	Glu	Asn	Gly 520	Val	Trp	Lys	Met	G1u 525	Ser	Ile	Phe	
Arg	Lys 530		Glu	Thr	Asp	Trp 535		Met	Val	Tyr	Leu 540		Arg	Lys	Glu	
G1y 545	Ser	Ser	Phe	Ala	Tyr 550		Ser	Trp	Lys	Phe 555	Glu	Cys	Gly	Ser	Val 560	
Gly	Leu	Lys	∀al	Asp 565	Ser	Ile	Ser	Ile	Arg 570	Thr	Ser	Ser	Gln	Thr 57.5	Phe	•
Gln	Thr	Gly	Thr 580	Val	Glu	Trp	Lys	Leu 585	Arg	Ser	Asp	Thr	A1 a 590	Gln	Val	
Glu	Leu	Thr 595	Gly	Asp	Asn	Ser	Leu 600	His	Ser	Tyr	Ala	Asp 605	Phe	Ser	Gly	
Ala	Thr 610	Glu	Val	Ile	Leu	G1u 615	Ala	Glu	Leu	Ser	Arg 620	Gly	Asp	Gly	Asp	
Va1 625	Ala	Trp	Gln	His	Thr 630	Gln	Leu	Phe	Arg	G1n 635	Ser	Leu	Asn	Asp	His 640	
Glu	Glu	Asn	Cys	Leu 645	Glu	Ile	He	Ile	Lys 650	Phe	Ser	Asp	Leu		÷	
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	gaa Glu	_	-				_						-	_	-	96
	cct Pro															144
-	gga Gly 50		_	-		_		-	_	-			_			192

160

	_					atg Met							_		_		240
						gct Ala		-	-			_					288
-			_	-		atg Met		_			-	_	-	•	•		336
				-		aca Thr				_			_	-			384
_			-	-	_	act Thr 135		-			-		_			,	432
						gac Asp	-		_	-				_	_		480
			-	-		tat Tyr	_	_	_	-	-	-	_	_	-		528
						ctt Leu											576
ggc Gly	ttc Phe	taa *															585

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<211> 194

<212> PRT

<213> Homo sapiens

<400> 114

161

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Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu Asn Tyr
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Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
                        55
Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
                    70
                                        75
Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser Pro Gly
                                 - 90
Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
                                105
Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
                            120
Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
                        135
Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
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                                        155
Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
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Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys Arg His
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Gly Phe
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_		_	_		_			_			_	_	ctg Leu			144
		-	_	-		_					-	-	gag G1u			192
-			_	_	-	-	_	-		-			cac His		•	240
_	_	-				_	_					_	ttc Phe	_		288
				-	_		_				-	_	cag Gln 110			336
										-			aaa Lys		-	384
					_								agc Ser	_	-	432
-			-			-	-		_	-	_		gag Glu	_		480
								-	-				999 Gly		-	528
			-					-	-				gcc Ala 190			576

				-						gtc Val				_	624
			-		_		-		-	cgc Arg 220		-			672
-	-	-			_				-	gcg Ala	-		_		720
										ctc Leu				-	768
			-	_	-		-		-	acc Thr					816
-	_	-	-	-		_			-	gtc Val	_	-		•	864
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<220>

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				cca Pro						144
				act Thr						192
				999 Gly 70						240
				aat Asn						288
				gtt Val						336
				aga Arg						384
				tac Tyr						432

166

				ctc Leu	_			-					-	-	_	480
				gtg Val 165				_				-	-			528
-		_		atc Ile			-						_			576
				cca Pro						-		-	_	_	-	624
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-			_	att Ile		_	_					_				720
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				gat Asp												816
-	gag Glu	-	tga *													828
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Thr Arg Lys Asn Ser Pro Leu His Tyr Tyr Gln Arg Leu Glu Ile Val
Glu Ala Ala Ile Arg Thr Leu Phe Ser Val Thr Gly Ile Leu Ala Glu
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Gln Phe Val Pro Asp Gly Pro His Leu His Leu Tyr His Glu Asn His
Trp Ile Lys Leu Met Asn Trp Gln His Ser Thr Met Tyr Leu Phe Phe
                                    90
Ala Val Ser Gly Ile Val Asp Met Leu Thr Tyr Leu Val Ser His Val
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Pro Leu Gly Val Asp Arg Leu Val Met Ala Val Ala Val Phe Met Glu
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Gly Phe Leu Phe Tyr Tyr His Val His Asn Arg Pro Pro Leu Asp Gln
                        135
                                            140
His Ile His Ser Leu Leu Leu Tyr Ala Leu Phe Gly Gly Cys Val Ser
145
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Ile Ser Leu Glu Val Ile Phe Arg Asp His Ile Val Leu Glu Leu Phe
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Arg Thr Ser Leu Ile Ile Leu Gln Gly Thr Trp Phe Trp Gln Ile Gly
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Phe Val Leu Phe Pro Pro Phe Gly Thr Pro Glu Trp Asp Gln Lys Asp
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Asp Ala Asn Leu Met Phe Ile Thr Met Cys Phe Cys Trp His Tyr Leu
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                        215
Ala Ala Leu Ser Ile Val Ala Val Asn Tyr Ser Leu Val Tyr Cys Leu
                   230
                                        235
Leu Thr Arg Met Lys Arg His Gly Arg Gly Glu Ile Ile Gly Ile Gln
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Lys Leu Asn Ser Asp Asp Thr Tyr Gln Thr Ala Leu Leu Ser Gly Ser
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					_					-	-		_	ggc Gly		144
														ggc Gly	-	192
		_	_			_	_		_					tac Tyr	-	240
							_	-		-		-	_	gta Val 95	-	288
													-	att Ile	-	336
_						_			-	_				gtt Val		384
														gtc Val		432
						_							_	ata Ile		480
														tgg Trp		528

169

	165	170	175
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		-	ta aga ctt cct aac 720 le Arg Leu Pro Asn 240
_	•		tt ctt ata acc atg 768 eu Leu Ile Thr Met 255
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Ile Ala Met	Thr Ala 85	Gly	Trp	Leu	Val	Leu 90	Ala	Ile	Ala	Met	Va1 95	Arg
Phe Tyr Met	Glu Lys 100	Gly	Thr	His	Arg 105	Gly	Leu	Tyr	Lys	Ser 110	Ile	G1n
Lys Thr Leu 115	_	Phe	Gln	Thr 120	Phe	Ala	Leu	Leu	Glu 125	Пe	Val	His
Cys Leu Ile 130	Gly Ile	Val	Pro 135	Thr	Ser	Val	Ile	Val 140	Thr	Gly	Val	G1n
Val Ser Ser 145	Arg Ile	Phe 150	Met	Val	Trp	Leu	Ile 155	Thr	His	Ser	Ile	Lys 160
Pro Ile Glr	Asn Glu 165		Ser	Val	Val	Leu 170	Phe	Leu	Val	Ala	Trp 175	Thr
Val Thr Glu	lle Thr 180	Arg	Tyr	Ser	Phe 185	Tyr	Thr	Phe	Ser	Leu 190	Leu	Asp
His Leu Pro 195	-	Ile	Lys	Trp 200	Ala	Arg	Tyr	Asn	Phe 205	Phe	Пe	Ilе
Leu Tyr Pro 210	Val Gly	Val	Ala 215	Gly	Glu	Leu	Leu	Thr 220	Ile	Tyr	Ala	Ala
Leu Pro His 225	Val Lys	Lys 230	Thr	Gly	Met	Phe	Ser 235	IJе	Arg	Leu	Pro	Asn 240
Lys Tyr Asr	Val Ser 245		Asp	Tyr	Tyr	Tyr 250	Phe	Leu	Leu	Ile	Thr 255	Met
Ala Ser Tyr	Ile Pro 260	Leu	Phe	Pro	G1n 265	Leu	Tyr	Phe	His	Met 270	Leu	Arg
Gln Arg Arg 275		Leu	His	Gly 280		Val		Val	G1u 285	Lys	Asp	Asp
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acc atc aag agg tcc agc cag acg ggc gag tgg cag aac att gcc atc
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Thr Ile Lys Arg Ser Ser Gln Thr Gly Glu Trp Gln Asn Ile Ala Ile
atg acc gag gag ccg gag ctg agc ccc gcc tac ctg atc agc gag gcc
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Met Thr Glu Glu Pro Glu Leu Ser Pro Ala Tyr Leu Ile Ser Glu Ala
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				-	aac Asn								_		96
					gtg Val										144
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		_		-	ttg Leu 70										240
	_				ggt Gly	_		-		-	-				288
	_		-		agc Ser	-		-							336
			-		ctg Leu										384
Leu	Ala	Lys	Trp	Tyr	gag G1u	Lys	Phe	Phe	Gly	Arg	Leu	Ser			432
_	-	-			gct Ala 150	-	_	_	-						480
		•	-		gtc Val		•	_		_					528
		-	-	_	cag G1n					_				_	576

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			ggg agc ggg ctg Gly Ser Gly Leu 220		672
		Leu Leu Val	agc agc acg agc Ser Ser Thr Ser 235		720
			a gct Éta gaa aag a Ala Leu Glu Lys 250	-	768
-			tct ctc gtc tgt Ser Leu Val Cys	~ ~	816
	y Pro Leu Arg		agc cgc ctc atc Ser Arg Leu Ile 285	His Gln Lys	864
			ccc tgg ctg gag Pro Trp Leu Glu 300		912
		Ser Ala Asp	ctg ggt gtc tgt Leu Gly Val Cys 315	-	960
			aag gtg gtg gac Lys Val Val Asp 330		1008
			ttc aag tgt tta Phe Lys Cys Leu		1056
			ttt gag gac tca Phe Glu Asp Ser		1104

174

355 360 365 gca gct cag ctg cag atg ctt ttc tca aac ttt cct gat ctg cgg gca 1152 Ala Ala Gln Leu Gln Met Leu Phe Ser Asn Phe Pro Asp Leu Arg Ala 370 375 380 1158 agc taa Ser * 385 <210> 124 <211> 385 <212> PRT <213> Homo sapiens <400> 124 Met Gln Tyr His Ala Leu Ser Leu Ala Met His Gly Phe Ser Val Thr Leu Leu Gly Phe Cys Asn Ser Lys Pro His Asp Glu Leu Leu Gln Asn Asn Arg Ile Gln Ile Val Gly Leu Thr Glu Leu Gln Ser Leu Ala Val Gly Pro Arg Val Phe Gln Tyr Gly Val Lys Val Val Leu Gln Ala Met 55 Tyr Leu Leu Trp Lys Leu Met Trp Arg Glu Pro Gly Ala Tyr Ile Phe Leu Gln Asn Pro Pro Gly Leu Pro Ser Ile Ala Val Cys Trp Phe Val 90 Gly Cys Leu Cys Gly Ser Lys Leu Val Ile Asp Trp His Asn Tyr Gly 105 Tyr Ser Ile Met Gly Leu Val His Gly Pro Asn His Pro Leu Val Leu 120 Leu Ala Lys Trp Tyr Glu Lys Phe Phe Gly Arg Leu Ser His Leu Asn 135 140 Leu Cys Val Thr Asn Ala Met Arg Glu Asp Leu Ala Asp Asn Trp His 150 155 Ile Arg Ala Val Thr Val Tyr Asp Lys Pro Ala Ser Phe Phe Lys Glu 165 170 Thr Pro Leu Asp Leu Gln His Arg Leu Phe Met Lys Leu Gly Ser Met 185 190 His Ser Pro Phe Arg Ala Arg Ser Glu Pro Glu Asp Pro Val Thr Glu 200 Arg Ser Ala Phe Thr Glu Arg Asp Ala Gly Ser Gly Leu Val Thr Arg

	210					215					220					
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Asp	Glu	Asp	Phe	Ser 245	Ile	Leu	Leu	Ala	A1a 250	Leu	Glu	Lys	Phe	G1u 255	Gln	
Leu	Thr	Leu	Asp 260	Gly	His	Asn	Leu	Pro 265	Seri	Leu	۷al	Cys	Val 270	Пe	Thr	
Gly	Lys	Gly 275	Pro	Leu	Arg	Glu	Tyr 280	Tyr	Ser	Arg	Leu	Ile 285	His	Gln	Lys	
His	Phe 290	Gln	His	Ile	Gln	Val 295	Cys	Thr	Pro	Trp	Leu 300	Glu	Ala	Glu	Asp	
Tyr 305	Pro	Leu	Leu	Leu	Gly 310	Ser	Ala	Asp	Leu	Gly 315	Val	Cys	Leu	His	Thr 320	
Ser	Ser	Ser	Gly	Leu 325	Asp	Leu	Pro	Met	Lys 330	Vạl	Val	Asp	Met	Phe 335	Gly	
Cys	Cys	Leu	Pro 340	Val	Cys	Ala	Val	Asn 345	Phe	Lys	Cys	Leu	His 350	G1u	Leu	
Val	Lys	His 355	Glu	Glu	Asn	Gly	Leu 360	Val	Phe	G1u	Asp	Ser 365	Glu	Glu	Leu	
Ala	A1a 370	Gln	Leu	Gln	Met	Leu 375	Phe	Ser	Asn	Phe	Pro 380	Asp	Leu	Arg	Ala	
Ser 385		•														
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	acg Thr 50	-		-			-			_		-		_	_	192
	tgc Cys	_		-				-	-	-			-			240
	999 Gly												_	_	_	288
-	cag Gln				-				-		-		-			336
-	caa Gln	_		-		_				-	-	-	_			384
	cca Pro 130	-		-	-	-	-	_					-			432
	ctt Leu	-			_				Asn						-	480
	cca Pro			-	-								-	_	-	528
	gat Asp		-			-							-			576
-	cag Gln		_			_	-					_	-			624

177

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330

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Arg	Thr 50	Val	His	Gln	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	Val
Tyr 65	Cys	Ser	Thr	Val	Va1 70	Pro	Ser	Asp	Asp	Va1 75	Thr	Val	Val	Tyr	G1n 80
Asn	Gly	Leu	Pro	Va1 85	Пе	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	G1u 95	Arg
Cys	Gln	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
Arg	Gln	Leu 115	Gln	Glu	Glu	Asp	Arg 120	Gly	Пe	Asp	Arg	Val 125	Ala	Ile	Tyr
Ser	Pro 130	Asp	Gly	Val	Arg	Val 135	Ala	Ala	Ser	Thr	Gly 140	Пe	Asp	Leu	Leu
Leu 145	Leu	Asp	Asp	Phe	Lys 150	Leu	Val	Ile	Asn	Asp 155	Leu	Thr	Tyr	His	Val 160
Arg	Pro	Pro	Lys	Arg 165	Asp	Leu	Leu	Ser	His 170	Glu	Asn	Ala	Ala	Thr 175	Leu
Asn	Asp	Val	Lys 180	Thr	Leu	Val	Gln	Gln 185	Leu	Tyr	Thr	Thr	Leu 190	Cys	Пe
Glu	Gln	His 195	Gln	Leu	Asn	Lys	G1u 200	Arg	G1u	Leu	Ile	G1u 205	Arg	Leu	Glu
Asp	Leu 210	Lys	Glu	Gln	Leu	Ala 215	Pro	Leu	Glu	Lys	Val 220	Arg	Ile	Glu	Ile
Ser 225	Arg	Lys	Ala	Glu	Lys 230	Arg	Thr	Thr	Leu	Va1 235	Leu	Trp	Gly	Gly	Leu 240
	_			245			_		250	Ala	_			255	•
Glu	Tyr	Ser	Trp 260	Asp	Ile	Met	G1u	Pro 265	Val	Thr	Tyr	Phe	11e 270	Thr	Tyr
Gly	Ser	A1a 275	Met	Ala	Met	Tyr	Ala 280	Tyr	Phe	Val	Met	Thr 285	Arg	Gln	Glu
Tyr	Val 290	Tyr	Pro	Glu	Ala	Arg 295	Asp	Arg	Gln	Tyr	Leu 300	Leu	Phe	Phe	His
Lys 305	Gly	Ala	Lys	Lys	Ser 310	Arg	Phe	Asp	Leu	Glu 315	Lys	Tyr	Asn	Gln	Leu 320
Lys	Asp	Ala	Пe	A1a 325	Gln	Gln	Lys	Trp	Thr 330	Leu	Arg	Asp			

WO 01/29221

179

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	His	Arg	Cys	His	Val	Cys	Asn	His	His	Phe	Gln		Lys	cag Gln		240	
	-	-		_						-	-			agt Ser 95	-	288	
														aca Thr		336	
atg	aaa	ctt	cat	cat	ggt	gag	aac	cgt	ctg	aag	aaa	ctc	atg	tgt	tgt	384	

PCT/US00/29052

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-	_				gac Asp							-	-		-	528
		Glu			ttg Leu											576
					cag Gln											624
		_	_		act Thr	-	_									672
					gga Gly 230											720
				_	aag Lys			_	-		-		-		-	768
				Lys	agg Arg											816
					gaa G1u											864
ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

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tgt Cys	cct Pro	ggc Gly	ctc Leu	cac His 325	acg Thr	ttt Phe	ctc Leu	ttg Leu	tgg Trp 330	tcc Ser	cat His	tca Ser	ggc Gly	ttt Phe 335	aac Asn	1008
tgc Cys	ctg Leu	ctt Leu	tgt Cys 340	gca Ala	gag Glu	atg Met	ctg Leu	gga Gly 345	cgg Arg	aaa Lys	gag Glu	gac Asp	ctc Leu 350	ctc Leu	cac His	1056
cac His	tgg Trp	aag Lys 355	cac His	cag Gln	cat His	aac Asn	tgt Cys 360	gag Glu	gac Asp	cct Pro	tcc Ser	aaa Lys 365	ctg Leu	tgg Trp	gct Ala	1104
att Ile	tta Leu 370	aat Asn	acg Thr	gtc Val	tcc Ser	aac Asn 375	cag Gln	gga Gly	gtg Val	atc Ile	gaa Glu 380	ctt Leu	tcc Ser	agt Ser	gaa Glu	1152
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Leu	Thr	Pro		Tyr	Leu	Gly	Cys		G]r	Asp	Asr	Ser		Ser	Pro	

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Trp 65	His	Arg	Cys	His	Val 70	Cys	Asn	His	His	Phe 75	Gln	Phe	Lys	Gln	His 80
Leu	Arg	Asp	His	Met 85	Asn	Thr	His	Thr	Asri 90	Arg	Arg	Pro	Tyr	Ser 95	Cys
Arg	Ile	Cys	Arg 100	Lys	Ser	Tyr	Val	Arg 105	Pro	Gly	Ser	Leu	Ser 110	Thr	His
	•	115					120	_				125	Met	_	
Glu	Phe 130	Cys	Ala	Lys	Val	Phe 135	Gly	His	Пe	Arg	Val 140	Tyr	Phe	Gly	His
Leu 145	Lys	Glu	Val	His	Arg 150	Val	Val	Ile	Ser	Thr 155	Glu	Pro	Ala	Pro	Ser 160
Glu	Leu	Gln	Pro	Gly 165	Asp	He	Pro	Lys	Asn 170	Arg	Asp	Met	Ser	Val 175	Arg
			180				_	185					Leu 190		
Asp	Phe	Leu 195	Leu	Asn	Gln	Ala	Asp 200	Glu	Val	Lys	Leu	G1n 205	Ile	Lys	Cys
Gly	Xaa 210	Cys	Gln	Ile	Thr	Ala 215	Gln	Ser	Phe	Ala	G1u 220	He	Lys	Phe	His
Leu 225	Leu	Asp	Val	His	Gly 230	Glu	Glu	Ile	Glu	Gly 235	Arg	Leu	Gln	Glu	G1y 240
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Ser	Pro	Asp	Trp 260	Lys	Arg	His	Pro	G1u 265	Arg	Gly	Lys	Pro	G1u 270	Lys	Val
His	Ser	Ser 275	Ser	Glu	Glu	Ser	His 280	Ala	Cys	Pro	Arg	Leu 285	Lys	Arg	Glr
Leu	His 290	Leu	His	Gln	Asn	Gly 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly
Pro 305	Gln	Ser	Gly	Thr	Asn 310	Lys	Pro	Arg	Glu	Thr 315	Cys	G1n	Gly	Pro	Glu 320
Cys	Pro	Gly	Leu	His 325	Thr	Phe	Leu	Leu	Trp 330	Ser	His	Ser	Gly	Phe 335	Asr
Cys	Leu	Leu	Cys 340	Ala	Glu	Met	Leu	Gly 345	Arg	Lys	Glu	Asp	Leu 350	Leu	His
His	Trp	Lys 355	His	Gln	His	Asn	Cys 360	Glu	Asp	Pro	Ser	Lys 365	Leu	Trp	Ala
Пe	Leu 370	Asn	Thr	Val	Ser	Asn 375	Gln	Gly	Val	Ile	G1u 380	Leu	Ser	Ser	Glu
Ala	Glu	Lys													

183

385

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		_	agg Arg				-		-		_		384
			atc Ile 135								_	_	432
			cca Pro	-			-		_				480
			 aat Asn	_	_		-				_		528
			ctg Leu			-			-				576
			gaa Glu										624
			aac Asn 215	_	_	-			-	_			672
-	-		atg Met		_	-	-	-	-			-	720
			atg Met										768
			gtt Val										816
			act Thr									-	864

								_	tat Tyr				_	-	9	912
			_	-		-			cct Pro 315						9	60
				_	-				gga Gly			-		_	10	800
			-	_					tat Tyr		-			_	10	56
		_	_			-		_	tct Ser	_		-			11	.04
			-	-					gga Gly		-	-			11	.52
-	_				-	_	-		cga Arg 395	-					12	200
		_	-				_		gtc Val						12	48
			-		-	-	_		agg Arg				_		12	96
									gct Ala			-	_		13	44
									gtt Val						13	92

			_	•	aag Lys 470		-		_			_	_			1440
					acc Thr		-		_			-	_	•		1488
	-	_			agg Arg		-		-		_	-			_	1536
				_	agc Ser	_	-	-								1584
-			-	-	gtt Val	-	_			-			-		-	1632
-			_		agt Ser 550			_		-	-	_				1680
_			_		ggt Gly		_	_	_	-		_		-		1728
	-	-	_		tta Leu	_	_		-	-				_		1776
					agc Ser											1824
	_	-		-	act Thr	-					-	_	•	•	•	1872
					gaa Glu 630											1920

			att Ile													1968
-		-	gaa Glu 660	-			-									2016
cct Pro	tga *															2022
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Ala	Cys	Pro	His 20	Met	Ala	Thr	Cys	Gly 25	Asn	Val	Leu	Phe	G1u 30	Gly	Arg	
Thr	Val	G1n 35	Leu	Gly	Lys	Leu	Cys 40		Thr	Gly	Val	G1u 45		Glu	Asp	
Asp	Glu 50		Thr	Glu	Ser	Asn 55		Ser	۷al	Glu	G1n 60		Ser	Val	Glu	
Va1 65		Asp	Gly	Pro	Thr 70		His	Asp	Pro	Asp 75		Tyr	Ile	Glu	Ile 80	
	Lys	Asn	Thr	Lys 85		Val	Pro	Glu	Tyr 90		Glu	Val	Ala	Tyr 95		
Asp	Tyr	Phe	Gly 100		Ile	Pro	Pro	Pro 105		Lys	Glu	Pro	Ile 110		Glu	
Arg	Pro	Tyr 115	Gly	Val	Gln	Arg	Thr 120		Пе	Ala	Gln	Asp 125		Glu	Arg	
Leu	Ile 130		Gln	Ser	Asp	Ile 135		Asp	Arg	Val	Val 140		Asp	Leu	Asp	
Asn		Asn	Tyr	Thr	Ile		Glu	Glu	Gly	Asp		Leu	Lys	Phe	Asn	
145					150					155					160	

Ser	Lys	Phe	Glu	Ser 165	Gly	Asn	Leu	Arg	Xaa 170	۷a٦	Пe	Gln	Ile	Arg 175	Lys
Asn	Glu	Tyr	Asp 180	Leu	Пe	Leu	Asn	Ser 185	Asp	Ile	Asn	Ser	Asn 190	His	Tyr
His	Gln	Trp 195	Phe	Tyr	Phe	Glu	Val 200	Ser	Gly	Met	Arg	Pro 205	Gly	Val	Ala
Tyr	Arg 210	Phe	Asn	Пe	IJе	Asn 215	Cys	Glu	Lys	Ser	Asn 220	Ser	Gln	Phe	Asn
Tyr 225	Gly	Met	Gln	Pro	Leu 230	Met	Tyr	Ser	Val	G1n 235	Glu	Ala	Leu	Asn	A1a 240
Arg	Pro	Trp	Trp	I1e 245	Arg	Met	Gly	Thr	Asp 250	Ile	Cys	Tyr	Tyr	Lys 255	Asn
			260	Ser				265				•	270	•	
•	•	275		Thr			280					285	•	•	
•	290			Tyr		295		•		•	300				
305			-	Leu	310					315				,	320
	-	•		Leu 325					330					335	
•			340	Ala				345					350		
		355		Arg		Ť	360					365		,	
Gly	G1u 370	Thr	Asn	Ala	Ser	Trp 375	Val	Met	Lys	Gly	Thr 380	Leu	Glu	Tyr	Leu
385				Pro	390					395					400
				Met 405					410					415	
Arg	Cys	Ser	Leu 420	Ser	Gly	Glu	Asp	Leu 425	Asn	Arg	Gln	Trp	G1n 430	Ser	Pro
Ser	Pro	Asp 435	Leu	His	Pro	Thr	11e 440	Tyr	His	Ala	Lys	G1y 445	Leu	Leu	Gln
Tyr	Leu 450	Ala	Ala	Val	Lys	Arg 455	Leu	Pro	Leu	Val	Tyr 460	Cys	Asp	Tyr	His
Gly 465	His	Ser	Arg	Lys	Lys 470	Asn	Val	Phe	Met	Tyr 475	Gly	Cys	Ser	Ile	Lys 480
Glu	Thr	Val	Trp	His 485	Thr	Asn	Asp	Asn	Ala 490	Thr	Ser	Cys	Asp	Va1 495	Val
Glu	Asp	Thr	Gly 500	Tyr	Arg	Thr	Leu	Pro	Lys	Ile	Leu	Ser	His 510	Ile	Ala

Pro	Ala	Phe 515	Cys	Met	Ser	Ser	Cys 520	Ser	Phe	Val	۷al	G1u 525	Lys	Ser	Lys	
Glu	Ser 530		Ala	Arg	Val	Va1 535		Trp	Arg	Glu	Ile 540		Val	Gln	Arg	
Ser 545	Tyr	Thr	Met	Glu	Ser 550	Thr	Leu	Cys	Gly	Cys 555	Asp	Gln	Gly	Lys	Tyr 560	
Lys	Gly	Leu	Gln	Ile 565	Gly	Thr	Arg	Glu	Leu 570	Glu	Glu	Met	Gly	A1 a 575	Lys	
Phe	Cys	Val	Gly 580	Leu	Leu	Arg	Leu	Lys 585	Arg	Leu	Thr	Ser	Pro 590	Leu	Glu	
Tyr	Asn	Leu 595	Pro	Ser	Ser	Leu	Leu 600	Asp	Phe	Glu	Asn	Asp 605	Leu	Ile	Glu	
Ser	Ser 610	Cys	Lys	Val	Thr	Ser 615	Pro	Thr	Thr	Tyr	Va1 620	Leu	Asp	Glu	Asp	
625					630			·		635			Ser		640	
				645					650	_	·		Glu	655		
	Gln	Glu	G1u 660	Val	Leu	Ser	Asp	Ser 665	Glu	Leu	Ser	Arg	Thr 670	Tyr	Leu	
Pro																
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	<2	220> 221> 222>		(3	375)											
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													Ile		tgt · Cys	40
													aca Thr 30			96
		-					-				-	-	att Ile			144

_	tat Tyr 50	-				_										192
	gga Gly	_	_			-										240
	gtt Val		-										-			288
_	ttt Phe		-													336
	tgg Trp	_			_			Gly		_		tga *				375
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Met 1	Ile	Gly	Pro	Ala 5	Val	Phe	Leu	Val	Ala 10	Ala	Gly	Phe	He	Gly 15	Cys	
-	Tyr	Ser	Leu 20	_	Val	Ala	Phe	Leu 25		Ile	Ser	Thr	Thr 30		Gly	
Gly	Phe	Cys 35		Ser	Gly	Phe	Ser 40		Asn	His	Leu	Asp 45		Ala	Pro	
Ser	Tyr 50		Gly	Пe	Leu	Leu 55		Ile	Thr	Asn	Thr 60		Ala	Thr	Ile	
Pro 65	Gly	Met	Va1	Gly	Pro 70		Ile	Ala	Lys	Ser 75		Thr	Pro	Asp	Asn 80	
	Val	Gly	Glu	Trp 85		Thr	Val	Phe	Tyr 90		Ala	Ala	Ala	11e 95		
Val	Phe	Gly	Ala 100		Phe	Phe	Thr	Leu 105		Ala	Lys	Gly	Glu 110		Gln	
Asn	Trp	Ala		Asn	Asp	His	His		His	Arg	His		110			

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	· </td <td>222></td> <td>(1)</td> <td>(</td> <td>ature 1485: ,C o</td> <td>)</td> <td></td>	222>	(1)	(ature 1485: ,C o)										
	ССС		gag		gga Gly									-	_	48
_		_	-	-	atc Ile					-	_					96
					gga Gly									-		144
			-		atg Met					_	-			-	atg Met	192
	Thr	Phe	Met	Asp	cca Pro 70	Gly	He	Phe	Pro	Arg	Ala	Glu	Glu		Glu	240
				-	ttc Phe	_	-									288
					cgc Arg	-										336
cgt	ссс	cct	cga	tgt	tcc	cac	tgc	agt	gtc	tgt	gac	aac	tgt	gtg	gag	384

WO 01/29221

Arg	Pro	Pro 115	Arg	Cys	Ser	His	Cys 120	Ser	Val	Cys	Asp	Asn 125	Cys	Val	Glu	
	ttt Phe 130															432
	tac Tyr															480
_	ggt Gly									_						528
-	ctc Leu			-	-	_	-	_								576
_	ggc Gly						-									624
	ctg Leu 210															672
	cgg Arg										-	-			_	720
	cgt Arg			_	_											768
_	aaa Lys		-			-										816
	tca Ser															864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	912

Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Ile	Thr	Glu	
-	cag G1n		_	_	-	_						-		-	_	960
	cgt Arg				_	_									-	1008
	agt Ser															1056
_	tat Tyr		-			_	-	_	_	_		-	-	_	_	1104
	tcc Ser 370		_	-	_	_	-	-		_	-		_			1152
	tca Ser				_		-									1200
_	ttg Leu	_			-		_							_		1248
	ttc Phe	-				_			_			_		_		1296
	cag Gln						_		_	_				-		1344
	ggc Gly 450							_	-	_	-		_		-	1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	1440

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 465 470 475 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu * 490 485 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr Val Pro 10 Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met 55 Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 70 75 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr 105 100 110 Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asn Cys Val Glu 120 125 Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg 135 Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 155 150 Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 170 Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val 185 Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

195

		195					200					205			
Val	Leu 210	Val	Ala	Arg	Gly	Arg 215	Thr	Thr	Asn	Glu	G1n 220	Val	Thr	Gly	Lys
Phe 225	Arg	Gly	Gly	Val	Asn 230	Pro	Phe	Thr	Asn	Gly 235	Cys	Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245	Ser	Ser	Pro	Ala	Pro 250	Arg	Tyr	Leu	Gly	Arg 255	Pro
Lys	Lys	Gļu	Lys 260	Thr	Ile	Val	Ile	Arg 265	Pro	Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	Пe	Thr	Va1 280	Lys	Ile	Met	Asp	Asn 285	Gly	Ile	Gln
Gly ·	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	He	Thr	G1u
Ser 305	Gln	Ser	Ala	Asp	Ala 310	Glu	Pro	Pro	Pro	Pro 315	Pro	Lys	Pro	Asp	Leu 320
Ser	Arg	Tyr	Thr	Gly 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	Glu
·			340				·	345					Thr 350		·
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Sen	Ser 360	Ser	Ser	Thr	Ser	A1 a 365	Ala	Met	Pro
His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	Ile	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	G1u	Pro 400
Ser	Leu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
His	Phe	Asp	Pro 420	Leu	Ser	Ser	Gly	Ser 425	Arg	Ser	Ser	Ser	Leu 430	Lys	Ser
Xaa	Gln	Gly 435	Thr	Gly	Phe	Glu	Leu 440	Gly	Gln	Leu	Gln	Ser 445	Ile	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	Ala 460	Asn	Gln	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
Asp	Phę	Glu	Ser	Va1 485	Gln	Ala	Gly	Leu	Ser 490	Gln	Thr	His	Leu		

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<213> Homo sapiens

<220>

196

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Met Val Gly Gly Asp Ala Asp Ala Arg Ser Lys Ala Leu Leu Gly Val
1 5 10 15

tgc gtc ggg tca ggc acg gaa gcc tat gtc ctg gta ttg gac cct cac

96

Cys Val Gly Ser Gly Thr Glu Ala Tyr Val Leu Val Leu Asp Pro His

20

25

30

tac tgg ggc act cca aaa agc ccc agt gaa cta cag gct gct ggg tgg
Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp
35 40 45

gtg ggc tgg caa gag gtg agt gca gcc ttt gac ccc aac tcc ttc tac
Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr
50 55 60

aac ctg tgc ttg acc agc ctt agc tcc caa cag cag cag cgc acc ttg
Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Gln Arg Thr Leu
65 70 75 80

gac tga 246 Asp *

<210> 136

<211> 81

<212> PRT

<213> Homo sapiens

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Cys Val Gly Ser Gly Thr Glu Ala Tyr Val Leu Val Leu Asp Pro His 20 25 30

Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp 35 40 45

Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr

50 55 60

Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Arg Thr Leu

65 Asp	••				70					75					80	
	<;			o sa	pien	S										
	<	220> 221> 222>	CDS (1)	(552)											
	gaa		cgg			gag Glu										48
						gct Ala					-					96
					-	gcg Ala			_	-	-					144
						aaa Lys 55								_	_	192
				_	-	gcg Ala	_	_		_		_				240
					-	att Ile		_	_	_	_		-	_	tct. Ser	288
						ttc Phe									-	336
						ctg Leu									-	384

		115					120					125				
					_		-	ggg Gly		_			_		•	432
	Glu			_	-	_		tct Ser						_	-	480
					Leu			gag Glu							-	528
	aga Arg		_	_		-	tag *									552
	<; <;	210> 211> 212> 213>	183	o sap	oiens	5										
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Met 1	Glu	Gln	Arg	Leu 5	Ala	Glu	Phe	Arg	Ala 10	Ala	Arg	Lys	Arg	Ala 15	Gly	•
Leu	Ala	Ala	G1n 20	Pro	Pro	Ala	Ala	Ser 25	Gln	Gly	Ala	Gln			Gly	
Glu	Lys	Ala											.30			
Lys			Giu	Ala	Ala	Ala		Leu	Lys	Ala	Ala		30 Gly	Trp	Leu	
		35				Lys	40		_		Ser	45	Gly	·		
Pro	,50	35 Phe	Leu	Val	Trp Glu	Lys 55	40 Pro	Leu	Pro	Ala Gln	Ser 60	45 A1a	Gly Arg	Ala	Gln Glu	
Pro 65	,50 Gly	35 Phe Leu	Leu Val	Val Gln Thr	Trp Glu 70	Lys 55 Ala	40 Pro Ala	Leu Arg	Pro Pro Pro	Ala Gln 75	Ser 60 Gly	45 Ala Ser	Gly Arg Thr	Ala Ser Gln	Gln Glu 80	
Pro 65 Thr	.50 Gly Pro	35 Phe Leu Trp	Leu Val Asn Asn	Val Gln Thr 85	Trp Glu 70 Ala	Lys 55 Ala Ile	40 Pro Ala Pro	Leu Arg Gln Leu Lys	Pro Pro Pro 90	Ala Gln 75 Ser	Ser 60 Gly Cys	45 Ala Ser Trp	Gly Arg Thr Asp Leu	Ala Ser Gln 95	Gln Glu 80 Ser	
Pro 65 Thr	.50 Gly Pro Leu	35 Phe Leu Trp Thr	Leu Val Asn Asn 100	Val Gln Thr 85 Ile	Trp Glu 70 Ala Thr	Lys 55 Ala Ile Phe	40 Pro Ala Pro Leu Glu	Leu Arg Gln Leu	Pro Pro Pro 90 Val	Ala Gln 75 Ser Leu	Ser 60 Gly Cys Leu	45 Ala Ser Trp Trp	Gly Arg Thr Asp Leu 110	Ala Ser Gln 95 Val	Glu 80 Ser Leu	
Pro 65 Thr Phe Leu	.50 Gly Pro Leu Gly	35 Phe Leu Trp Thr Leu 115	Leu Val Asn Asn 100 Phe	Val Gln Thr 85 Ile Val	Trp Glu 70 Ala Thr Glu	Lys 55 Ala Ile Phe Leu	40 Pro Ala Pro Leu Glu 120	Leu Arg Gln Leu Lys 105	Pro Pro Pro 90 Val	Ala Gln 75 Ser Leu Leu	Ser 60 Gly Cys Leu Ala	45 Ala Ser Trp Trp Tyr 125	Gly Arg Thr Asp Leu 110 Phe	Ala Ser Gln 95 Val	Glu 80 Ser Leu Leu	

145 Ala	Ile	Gln	Gly		150 Leu	Thr	Ala	Glu		155 Leu	Glu	Arg	Glu		160 Gln	
Leu	Arg	Pro	Leu 180	165 Ala	Gly	Arg			170					175		
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	<	220> 221> 222>	CDS (1)	(9	912)											
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-				-	_	aac Asn		_				_		_		96
_	_	_				gct Ala	-				-				-	144
-			_			cgg Arg 55					-				_	192
						gct Ala					Phe					240
-			_			ctc Leu						_				288
						gac Asp								_	-	336

_	-				_	-			_	-	tca Ser		-			384
-	-	_		•							tca Ser 140			•		432
		_					_			-	tca Ser		-			480
	-		_	-	-	-	-		_		cta Leu	-	-		_	528
			_			_	-		-		cct Pro	_		_		576
		_	-	_		_	-		-		aaa Lys					624
-	_		-	-	-	-		-	-		ggt Gly 220				•	672
		-			-	-			_		tgg Trp		_	-	_	720
							-	_	-	_	aaa Lys	_			cag · Gln	768
								-			gat Asp		-	_	-	816
							-			-	gat Asp		-	_		864

201

912

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Thr Arg Ser Arg Asp Arg Ser Leu Leu Pro Ser Asp Asp Glu Leu Lys

			260					265					270			
Trp	Gly	A1a 275	Lys	Glu	Val	Glu	Asp 280	His	Tyr	Cys	Asp	Ala 285	Cys	Gln	Phe	
Ser	Asn 290	Arg	Phe	Pro	Arg	Trp 295	Val	Pro	Trp	Met	Val 300	Lys	Ser	Glu		
		210> 211> 212> 213>	750 DNA	o sar	oiens	S										
	<'	220> 221> 222>		(7	750)											
-	ggt		CCC			gcg Ala							-	_		48
			-	-		tgc Cys				_						96
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Leu	Thr 50	Asp	Gly	Ser	Tyr	Asp 55	Asp	Val	Leu	Asn	Ala 60	Glu	G1n	Leu	Gln
Lys 65	Leu	Leu	Tyr	Leu	Leu 70	Glu	Ser	Thr	Glu	Asp 75	Pro	Val	Ile	Ile	G1u 80
Arg	Ala	Leu	Ile	Thr 85	Leu	Gly	Asn	Asn	A1 a 90	Ala	Phe	Ser	Val	Asn 95	G1n
Ala	Ile	Пе	Arg 100	Glu	Leu	Gly	Gly	Ile 105	Pro	Ile	Val	Ala	Asn 110	Lys	Пe
Asn	His	Ser 115	Asn	Gln	Ser	He	Lys 120	Glu	Lys	Ala	Leu	Asn 125	Ala	Leu	Asn
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-					gac Asp		-	-		-	-	-	-	_		528

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Glu	Trp 50	Lys	Gly	Trp	Ser	Lys 55	Pro	Ser	Asp	Ser	Pro 60	Ala	Ala	Leu	Glu
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Tyr	Asp	Glu 115	Asp	Phe	Ala	Gly	Gly 120	Met	Asp	Thr	Asp	Met 125		Gly	Gln
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Gln	Thr	Val	Ser	Pro 165	Asp	Thr	Leu	Cys	Ser 170	Ser	Leu	Cys	Ser	Leu 175	
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Lys	Asp	Cys	Gln	Pro 245	Leu	Cys	Pro	Pro	Leu 250	Thr	Gly	Ser	Trp	G1u 255	Arg
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				gag Glu	_	-									480
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				_	-	gta Val							_	-	-	576
-	_				_	999 Gly		-					-	-		624
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		-		_	_	gcc Ala					-	-			-	720
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-							_		-				gct Ala	-	-	1248
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Leu	Thr	Tyr 115	Ser	Leu	Cys	Cys	Leu 120	Thr	Lys	Leu	Ser	G1n 125	Asp	Tyr	Phe
Val	Leu 130	Leu	Val	Gly	Arg	Ala 135	Leu	Gly	Gly	Leu	Ser 140	Thr	Ala	Leu	Leu
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Asp	Phe	Pro	Ala	G1u 165	Trp	Ile	Pro	Ala	Thr 170	Phe	Ala	Arg	Ala	Ala 175	Phe
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Val	Leu	Asp 275	Pro	His	Gly	Ala	Pro 280	Leu	Gly	Ile	Пe	Phe 285	Ser	Ser	Phe
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Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn 50 55 60

Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg 65 70 75 80

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48

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Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
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Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
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 Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
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Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
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Ser Ser Thr Leu Ala Arg Lys Glu Ala Gly Gly Arg Arg Lys Arg Val
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Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
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Pro Val Gly Ala Pro Ala Val Gln Ser Ile Leu Val Ala Gly Glu Glu
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			gat Asp												288
-			gag Glu 100			_	_				-	_	-		336 ⁻
			ctg Leu	 _			_		_		-				384
-		_	agt Ser			-					-	-			432
			cag Gln									-		-	480
-		_	atg Met		-	_	_	-	-	-	•				528
			aac Asn 180												576

					tta Leu									_		624
					cac His											672
	Leu				tcc Ser 230								-		_	720
	aac Asn	_	_	tga *					,							735
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	ggg Gly					-						-			-	336
	tcc Ser				-	-				_		_		-		384
	tac Tyr 130	_		-		-	-	-					-			432
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	gag Glu															576
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Pro	Ser	Cys	Thr	Va1 245	G1y	Phe	Tyr	Ala	Gly 250	Asp	Arg	Lys	Glu	Phe 255	Glu	
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_	cgg Arg												Gln	-		864
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Glu	Thr	Leu	Asn	Pro 165	Val	Tyr	Val	Pro	Cys 170	۷a٦	Lys	Glu	Leu	Leu 175	Arg
Cys	Glu	Leu	Cys 180	Leu	Gly	Ile	Met	Gly 185	Gly	Lys	Pro	Arg	His 190	Ser	Leu
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Thr	Leu	Cys	Ser 260	Glu	Leu	Thr	Arg	Val 265	Leu	Ser	Ser	Ser	Ser 270	Ala	Thr
Glu	Arg	Tyr 275	Pro	Met	Phe	Thr	Leu 280	Ala	Glu	Gly	His	A1 a 285	Gln	Asp	His
Ser	Leu 290	Asp	Asp	Leu	Cys	Ser 295	Gln	Leu	Ala	Gln	Pro 300	Thr	Leu	Arg	Leu
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	-						-					gac Asp				432
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Met	Leu	Thr	Leu 100	Thr	Tyr				Lys	Glu	Tyr	Ser	Pro 110	Arg	Arg	
Leu	Trp	Trp 115								Leu	Ser	Val 125		Gly	Ile	
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	Gln	Gln	Val	Leu 165		Glu	Ala	Ser	Gln 170		Asn	Leu	Leu	Ala 175		
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					cgc Arg 70											240
					cac His										_	288
gcc Ala					gga Gly		_	_								336

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													agc Ser		-	4	132
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Ile 65		Leu	Arg	Met	Arg 70		Хаа	Lys	Gly	Asp 75		Asp	Leu	Tyr	Va1 80		

Ser	Ala	Ser	Ser	Leu 85	His	Pro	Ser	Phe	Asp 90	Asp	Tyr	Glu	Leu	G1n 95	Ser	
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Pro	Ser	Gly 115	His	Arg	Arg	Leu	Trp 120	Thr	Pro	Leu	Pro	Pro 125	Gly	Glu	Arg	
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		-			gag Glu	-			-		-	-			336
-					cta Leu								_		384
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					ata Ile			-		-		_	_	_	528
					gca Ala								-	-	576
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_			aac Asn		-			_	-	_		-	-	960
-		-	cag G1n	_	_	 -	_		_	_	-			1008
	-		acg Thr 340	-	-	_				 _		-	-	1056
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	_		_		_			_				-	-	gct Ala	-	;	336
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		_			ctc Leu 70	-										240
					aat Asn											288
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									cag Gln		_		-			816	
gag	ctc	999	gtc	cťt	ttc	ctc	cct	tca	gca	ttt	ggt	cta	gac	agt	ttc	864	

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Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
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Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
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Tyr Lys *

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Ser Thr Thr Val Ser Arg Lys Ala Trp Gly Ala Glu Ala Val Gly Cys 50 55 60

Ser Ile Gln Leu Thr Thr Pro Val Asn Val Leu Val Ile His His Val 65 70 75 80

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Tyr Lys

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	ctg Leu 210			-	_	_			_				_			672
	gat Asp															720
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	cag Gln	-	_	-			-								-	816
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_			-			aca Thr			_			-	_	-		480
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Cys	Asp	Arg		Val	۷aΊ	Asn	Gly	He	Ile	Ala	Thr	۷a1		Val	Ser	
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+		5 + -	-+-	+			-+-	-++	+	-++	5 + 5	-++	-+-			144
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		-			gga Gly	_		_								288

258

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gca atg gct ttc cag gtc cca ccc aac tca ccc cag ggg agt gtg gcc
                                                                      336
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
            100
                                105
                                                     110
tgc ccg ccc cct cca gcc tac tgc aac acg cct ccg ccc ccg tac gaa
                                                                      384
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
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                            120
                                                125
cag gta gtg aag gcc aag tag
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Gln Val Val Lys Ala Lys *
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Pro Leu His Thr Glu Ala Val Val Leu Leu Val Pro Ser Asp Asp Gly
Arg Ala Phe Leu Leu Arg Xaa Gly Phe Phe Ile Arg Arg Met Tyr
                            40
                                                45
Pro Pro Pro Leu Ile Glu Glu Pro Ala Phe Asn Val Ser Tyr Thr Arg
                        55
Gin Pro Pro Asn Pro Gly Pro Gly Ala Gin Gin Pro Gly Pro Pro Tyr
Tyr Thr Asp Pro Gly Gly Pro Gly Met Asn Pro Val Gly Asn Ser Met
                85
                                    90
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
                                105
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
                            120
Gln Val Val Lys Ala Lys
    130
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			(1)	_													
					,C or	^ G											
	,	100>	102														
at.a				ttc	cag	aca	act.	cta	taa	tta	cta	cad	ccg	ааа	at.c	4	18
		_											Pro				
1				5					10					15			
atc	ttc	atc	cta	aaa	gat	atc	ttt	gat	gaa	aaa	aaq	taa	agc	acc	cct	g	96
			_										Ser			_	
			20		·			25					30				
naa	acc	taa	aca	qat	gat	ata.	aaa	caa	ttt	caq	aaa	atq	ttc	aga	cac	14	14
_	_			-	-					_		_	Phe	_		_	
		35					40					45					
сса	aqt	cat	ata	caq	cta	aaq	gta	att	act	gga	aac	cat	gac	att	aac	19) ₂
	_		-	_	_	-	-	_	_				Asp				_
	50					55				·	60		•				
ttc	cat	tat	gag	ato	aac	aca	tac	aaa	ata	gaa	cac	t.t.t.	gag	aaa	ata	24	1(
				-					_	-	-		Glu				•
65					70			-y -		75	3			-5 -	80		
TT.		1.1						.							_4_	0.0	٠,
															atg Met	. 28	52
rne	261	361	ulu	85	Leu	FIIC	261	пρ	90	uly	116	Mail	THE	95	net.		
									_								
													tgc			33	}6
Val	Asn	Ser		Ala	Leu	Asn	Gly		Gly	Cys	Gly	He	Cys	Ser	Glu		
			100					105					110				
aca	gaa	gca	gag	ctc	att	gaa	gtt	tct	cac	aga	ctg	aac	tgc	tcc	cga	38	32
Thr	Glu		Glu	Leu	Пe	Glu		Ser	His	Arg	Leu		Cys	Ser	Arg		
		115					120					125					

					_							_	ccc Pro	_	432
	_		_		_	_						_	agt Ser	-	480
-		_			_	_	_	-	_	-	-		gac Asp 175		528
		-	-			-							caa G1n	-	576
	-				_	_	_	_					acg Thr		624
													agc Ser		672
			_				_			_			atg Met		720
_		-			_				_	_			cca Pro 255	_	768
	-		-	_				-	 				ctt Leu		816
-									-				ctt Leu		864
			_			aag Lys 295	-	-		tga *					900

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Xaa Ala Trp Ala Asp Asp Val Glu Arg Phe Gln Lys Met Phe Arg His
Pro Ser His Val Gln Leu Lys Val Val Ala Gly Asn His Asp Ile Gly
                        55
Phe His Tyr Glu Met Asn Thr Tyr Lys Val Glu Arg Phe Glu Lys Val
Phe Ser Ser Glu Arg Leu Phe Ser Trp Lys Gly Ile Asn Phe Val Met
                85
                                    90
Val Asn Ser Val Ala Leu Asn Gly Asp Gly Cys Gly Ile Cys Ser Glu
                                105
Thr Glu Ala Glu Leu Ile Glu Val Ser His Arg Leu Asn Cys Ser Arg
                            120
Glu Ala Arg Gly Ser Ser Arg Cys Gly Pro Gly Pro Leu Leu Pro Thr
Ser Ala Pro Val Leu Leu Gln His Tyr Pro Leu Tyr Arg Arg Ser Asp
                    150
                                        155
Ala Asn Cys Ser Gly Glu Asp Ala Ala Pro Ala Glu Glu Arg Asp Ile
                165
                                    170
                                                        175
Pro Phe Lys Glu Asn Tyr Asp Val Leu Ser Arg Glu Ala Ser Gln Lys
                                185
Leu Leu Trp Trp Leu Gln Pro Arg Leu Val Leu Ser Gly His Thr His
                            200
Ser Ala Cys Glu Val His His Gly Gly Arg Val Pro Glu Leu Ser Val
                        215
                                            220
Pro Ser Phe Ser Trp Arg Asn Arg Asn Asn Pro Ser Phe Ile Met Gly
                    230
                                        235
Ser Ile Thr Pro Thr Asp Tyr Thr Leu Ser Lys Cys Tyr Leu Pro Arg
```

				245					250					255		
Glu	Asp	Val	Val 260		Пe	Ile	Tyr	Cys 265		Val	۷al	Gly	Phe 270	Leu	Val	
Val	Leu	Thr 275	Leu	Thr	His	Phe	G1y 280	Leu	Leu	Ala	Ser	Pro 285	Phe	Leu	Ser	
Gly	Leu 290	Asn	Leu	Leu	Gly	Lys 295	Arg	Lys	Thr	Arg						
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			tgt Cys													48
			tca Ser 20				-	-	_		_					96
			ggc Gly				_	-			-					144
			tct Ser													192
			gat Asp			-							_			240
			tat Tyr	-			-			-	-	-			-	288
			gta Val	_	_		_							_	_	336

263

100 105 110 cga ctt tgt tac ctg aaa gag cag gaa gat att gca tgg tct gct ctt 384 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 115 120 125 gtg aag ttg ttt gat ccc gtg aaa tct ccc aga tgt tat gct gtt att 432 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 140 135 gcc ctg aag aag cag cag tga 453 Ala Leu Lys Lys Gln Gln * 145 150 <210> 186 <211> 150 <212> PRT <213> Homo sapiens <400> 186 Met Ser Ala Cys Leu Ala Leu Glu Arg Val Ala Ala Gly Gln Gly Leu Pro Thr Glu Ser Leu Phe Tyr Arg Ala Val Leu Gln Asp Ile Ile Lys 25 Asp Cys Tyr Gly Ile Thr Lys Cys Asp Arg His Val Gly Lys Ile Tyr 40 Ser Lys Cys Ser Ser Phe Leu Asp Tyr Val Arg Arg Ser Leu Lys Lys 55 Leu Gly Leu Asp Glu Ser Lys Leu Pro Glu Lys Ile Ile Met Asn Tyr Tyr Glu Lys Tyr Lys Pro Arg Met Asn Glu Leu Glu Ala Phe Asn Met 90 Leu Lys Val Val Leu Ala Pro Cys Ile Glu Thr Leu Ile Leu Leu Asp 105 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 125 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 Ala Leu Lys Lys Gln Gln 145 150 <210> 187

<211> 1491

264

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														aat Asn	-	480
-				_										gtt Val 175		528
	_			-			-						-	gac Asp		576
-		-					_	_	-		-			cac His		624
														gct Ala		672
,	-		-						Asp					gcc Ala	-	720
														cca Pro 255		768
_		-				_								aag Lys		816
	_		-	-		-		-	-					gac Asp		864
					-				-	_	_	_		aac Asn		912
-														act Thr		960

	999 Gly				-		-					_		_		1008
	cct Pro										_		-	-		1056
-	gtc Val	_	_						_		-				-	1104
	agc Ser 370	-	_	-	-								_	-	-	1152
	cac His		_	_			-			-			_	-	-	1200
-	gtg Val	-	_		-	-		_		Thr	-	-	-	-		1248
	acc Thr		-		-	-			_		-					1296
_	act Thr			-		-					_					1344
	cca Pro 450															1392
	gta Val			-											-	1440
	att Ile															1488

1491

267

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225

230

Asn Met Leu Glu Val Phe Val Ser Ser Leu Glu Glu Phe Gln Pro Asp

Leu Val Val Leu Ser Gly Leu His Met Met Glu Gly Gln Ser Lys Glu

			260					265					270			
Leu	Gln	Arg 275	Lys	Arg	Leu	Leu	G1u 280	Val	Val	Thr	Ser	Ile 285	Ser	Asp	Ile	
Pro	Thr 290	Gly	Ile	Pro	Val	His 295	Leu	Glu	Leu	A.la	Ser 300	Met	Thr	Asn	Arg	
G1u 305	Leu	Met	Ser	Ser	Ile 310		His	Gln	Val	Phe 315		A٦a	Val	Thr	Ser 320	
		Leu	Asn	G1u 325		Ġlu	Leu	Leu	Phe 330		Thr	Gln	Ser	A1 a 335		
Gly	Pro	His	Ser 340		Leu	Ser	Ser	Trp 345		Gly	Val	Pro	Asp 350		Gly	
Met	Val	Ser 355		Пe	Leu	Phe	Trp 360		Leu	Lys	Glu	His 365		Arg	Ser	
Lys	Ser 370		Ala	Ser	Asp	Leu 375		Arg	Пe	His	Phe 380	His	Thr	Leu	Val	
Tyr 385		Пe	Leu	Ala	Thr 390		Asp	Gly	His	Trp 395		Asn	Gln	Leu	Ala 400	
	Val	Ala	Ala	Gly 405		Arg	Val	Ala	Gly 410		Gln	Ala	Cys	Ala 415		
Glu	Thr	Пе	Asp 420		Ser	Arg	۷al	Ser 425		Arg	Ala	Pro	G1n 430		Phe	
Met	Thr	Ser 435		Ser	Glu	Ala	Gly 440		Arg	He	۷a۱	Leu 445		Pro	Asn	
Lys	Pro 450		Val	Glu	Trp	His 455		Glu	Gly	Ile	Ser 460	Phe	His	Phe	Thr	
Pro 465	Val	Leu	Val	Cys	Lys 470	Asp	Pro	Ile	Arg	Thr 475	Val	Gly	Leu	Gly	Asp 480	
Ala	Ile	Ser	Ala	G1u 485	Gly	Leu	Phe	Tyr	Ser 490	Glu	Val	His	Pro	His 495	Tyr	
	<2 <2	210> 211> 212> 213>	339 DNA	o sap	oiens	5										
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				-		_			-			Ile				+0

269

	ggt Gly												96
	gcg Ala	_				-	-				-		144
_	tgt Cys 50	_											192
	tac. Tyr		_	-									240
	tgg Trp			-	_	-	-						288
	atc Ile												336
tga *													339

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<211> 112

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<213> Homo sapiens

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Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 20 25 30

Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 35 40 45

Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 50 55 60

Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser

65					70					75					80	
Pro	Trp	Thr	He	Thr 85	Gln	Met	Val	Ile	G1 <i>y</i> 90	Leu	Ser	Ile	Ala	Thr 95	Trp	
Gly	Ile	Val	Val 100	Met	Ala	Asp	Pro	Lys 105		Lys	Ala	Tyr	Arg 110	Val	Val	
	<;			o sar	oi en:	S										
	<	220> 221> 222>	CDS (1)	(6	530)											
		400>					•									
			gcc Ala													48
			gcg Ala 20													96
			ctt Leu													144
			cca Pro													192
			gtt Val													240
			gtg Val													288
			ttt Phe 100													336

271

gga gag aga att cga ctg gag aag gtc ctg ctg gtt ggg gca gac aac Gly Glu Arg Ile Arg Leu Glu Lys Val Leu Leu Val Gly Ala Asp Asn 130							tta Leu										384
Phe Thr Leu Leu Gly Lys Pro Leu Leu Gly Lys Asp Leu Val Arg Val 150 155 160 gaa gcc aca gtc att gaa aag aca gaa tca tgg cca aga atc att atg Glu Ala Thr Val Ile Glu Lys Thr Glu Ser Trp Pro Arg Ile Ile Met 165 170 175 aga ttc agg aaa agg aaa aac ttc aag aag aaa aga atc gtc acg acc Arg Phe Arg Lys Arg Lys Asn Phe Lys Lys Lys Arg Ile Val Thr Thr 180 185 190 ccg cag act gtc ctc cgg ata aac agc att gag att gct ccg tgt ttg Pro Gln Thr Val Leu Arg Ile Asn Ser Ile Glu Ile Ala Pro Cys Leu 195 200 205		Glu				_	Glu					Val		-	-		432
Glu Ala Thr Val Ile Glu Lys Thr Glu Ser Trp Pro Arg Ile Ile Met 165 170 175 aga ttc agg aaa agg aaa aac ttc aag aag aaa aga atc gtc acg acc Arg Phe Arg Lys Arg Lys Asn Phe Lys Lys Lys Arg Ile Val Thr Thr 180 185 190 ccg cag act gtc ctc cgg ata aac agc att gag att gct ccg tgt ttg Pro Gln Thr Val Leu Arg Ile Asn Ser Ile Glu Ile Ala Pro Cys Leu 195 200 205	Phe		_			Lys					Lys	_		-	-	Val	480
Arg Phe Arg Lys Arg Lys Asn Phe Lys Lys Lys Arg Ile Val Thr Thr 180 185 190 ccg cag act gtc ctc cgg ata aac agc att gag att gct ccg tgt ttg Pro Gln Thr Val Leu Arg Ile Asn Ser Ile Glu Ile Ala Pro Cys Leu 195 200 205		-		_	Пe	_	_		-	Ser			_		Ile	-	528
Pro Gln Thr Val Leu Arg Ile Asn Ser Ile Glu Ile Ala Pro Cys Leu 195 200 205 ttg tga				Lys					Lys					Val	_		576
· · ·		_	Thr	-				Asn	_				Āla	_	_	_	624
	_	-															630

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<212> PRT

<213> Homo sapiens

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 Leu Ala Ser Ala Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly 25
 30

 Ala Ala Ser Leu Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln Ser Thr 35
 40
 45

 Ser Tyr Leu Pro Gly Tyr Val Pro Lys Thr Ser Leu Ser Ser Pro Pro 50
 55
 60

 Trp Pro Glu Val Val Leu Pro Asp Pro Val Glu Glu Thr Arg His His

65					70					75					80	
Ala	Glu	Val	۷a۱	Lys 85	Lys	Val	Asn	Glu	Met 90	Пe	Val	Thr	Gly	G1n 95	Tyr	
Gly	Arg	Leu	Phe 100	Ala	Val	Val	His	Phe 105	Ala	Ser	Arg	Gln	Trp 110	Lys	Val	
Thr	Ser	Glu 115	Asp	Leu	Ile	Leu	Ile 120	Gly	Asń	Glu	Leu	Asp 125	Leu	Ala	Cys	
,	130			_		135	-				140	•	Ala	•		
145					150					155			Val		160	
				165					170	·		_	Ile	175		
			180					185					Val 190			
	GIn	1hr 195	Val	Leu	Arg	He	Asn 200	Ser	He	Glu	He	A1a 205	Pro	Cys	Leu	
Leu																
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							-					-	acc Thr	-		144
		_					_						ggc G1v			192

273

50 55 60 gtg tac tgg gtg gca cgg aag ccc atg aag atg gga tac ccc ccg agt 240 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 65 70 75 cca tgg acc att acg cag atg gtc atc ggc ctc agt gag aat caa ggc 288 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 85 90 att gcc acc tgg ggt atc gtt gtc atg gca gac ccc aaa ggg aag gcc 336 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 tac cgc gtt gtt tga 351 Tyr Arg Val Val * 115 <210> 194 <211> 116 <212> PRT <213> Homo sapiens <400> 194 Met Gly Ser Arg Leu Ser Gln Pro Phe Glu Ser Tyr Ile Thr Ala Pro 5 10 15 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 25 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 40 Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 55 - 60 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 70 75 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 90 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 110 Tyr Arg Val Val 115 <210> 195 <211> 1047

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											tta Leu 30				96
											tac Tyr			1	.44
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					_						cac His	_		2	240
											agt Ser			2	88
											tca Ser 110			3	36
											gca Ala			3	84
Pro										-	 gcg Ala	-		4	32

-	-	-	-			gac Asp						_			480
	_			-		gag Glu	_					-			528
	_					atg Met							_		576
			_	-	-	act Thr		-	-					-	624
_			-	-	-	gcc Ala 215					_			_	672
						ttg Leu								_	720
						acc Thr	-	_	-						768
		-			_	gcc Ala	-				_	_		-	816
-						att Ile								-	864
						caa Gln 295									912
						gac Asp									960

276

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 tgg cta att cca gga caa gag cag gaa cat gtg gag tag 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu * 340 345 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu 10 Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu 90 Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 135 140 130 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 150 155 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 205 200 Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala 215 Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

225					230					235					240	•	
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Val 250	Pro	Asn	Пe	Leu	Leu 255	Phe	•	
G1n	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265	Asn	His	Thr	Asp •	Arg 270	Thr	Leu		
Glu	Thr	Leu 275	Lys	Ile	Phe	Ile	Phe 280	Asn	Gln	Thr	Gly	I1e 285	Glu	Ala	Lys		
Lys	Asn 290	Val	Val	Val	Thr	G1n 295	Ala	Asp	Gln		Gly 300	Pro	Leu	Pro	Ser		
Thr 305	Leu	Ile	Lys	Ser	Val 310	Asp	Trp	Leu	Leu	Val 315	Phe	Ser	Leu	Phe	Phe 320	•	
Leu	Ile	Ser	Phe	Ile 325	Met	Tyr	Ala	Thr	Ile 330	Arg	Thr	Glu	Ser	11e 335	Arg		
Trp	Leu	Ile	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu						
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	<2	220> 221> 222>	CDS (1)	(4	144)												
ata		400>		220	220	aaa	ctt	Cad	aat	c++	ata	act	003	200	ato		48
						Lys											40
						gga Gly									_		96
						aaa Lys											144
				_	-	ggc Gly 55	-							_	-		192
						gtg Val									_		240

65					70					75					80		
				_	gga Gly	_				_	_		_	-	_	·	288
-				-	gaa Glu							_	-		-	;	336
_				-	cca Pro				-		-					;	384
_	-		-	_	gcg Ala		-		_							•	432
	ctg Leu		tga *													•	444
	<2 <2	210> 211> 212> 213>	147 PRT	o sap	oiens	5											
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Met 1	Ala	Phe	Pro	Lys 5	Lys	Lys	Leu	Gln	Gly 10	Leu	Val	Ala	Ala	Thr 15	Ile		
Thr	Pro	Met	Thr 20	Glu	Asn	Gly.	Glu	I1e 25	Asn	Phe	Ser	Val	Ile 30	Gly	Gln		
Tyr	Val	Asp 35		Leu	Val	Lys	Glu 40		Gly	Val	Lys	Asn 45		Phe	Val		
Asn	G1y 50		Thr	Gly	Glu	Gly 55	. •	Ser	Leu	Ser	Va1 60		Glu	Arg	Arg		
G1n 65		Ala	Glu	Glu	Trp 70		Thr	Lys	Gly	Lys 75		Lys	Leu	Asp	G1n 80		
	Ile	Ile	His	Va1 85	Gly	Ala	Leu	Ser	Leu 90		Glu	Ser	Gln	G1u 95			
Alá	Gln	His	Ala 100		Glu	Пе	Gly	Ala 105		Gly	Пе	Ala	Val 110		Ala		
Dra	Dha	Dhe		Lvc	Dro	Trn	Thr		Acn	Πρ	الم ا	Πe		Dhe	Lau		

-	Glu 130 Leu		Ala	Ala	Ala	Pro .135	120 Leu	Pro	Cys	His	Phe 140	125 Ile	Thr	Ile	Thr	
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	_	-	-		-		-	_			-			ttg Leu	_	96
	-	-					-		-					gtg Val	-	144
														gtt Val		192
														tcc Ser		240
		_		-			_							ctg Leu 95		288

			tat Tyr							336
			cct Pro				_	_	•	. 384
			cct Pro 135							432
			tgg Trp							480
			cgg Arg					 	•	528
			ctg Leu							576
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			gtt Val 215							672
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<213> Homo sapiens

<220>

<221> VARIANT

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<400> 200

WO 01/29221

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<210> 201

<211> 885

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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<221> misc_feature <222> (1)...(885) <223> n = A.T.C or 6

145

150

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155

			cgc Arg					_					•			528
	-		cat His 180		 _	-		-	_	_		_				576
			act Thr							-				-		624
	-		ttg Leu	-		-	-	_		-		-	_			672
			gtg Val						-		_	_				720
			aaa Lys	-				-			_	_	~ ~	•		768
			tac Tyr 260			-			-					-	,	816
-		-	atg Met		_	-	-	-	-				•			864
	-		gga Gly		tga *											885

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<211> 294

<212> PRT

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<220>

284

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	gtt Val											-	-	-	96
	ctc Leu														144
	tct Ser 50	_	_					_		_	_	-	-	-	192
_	gct Ala				-		-	_					_		240
-	ctg Leu					-		_	_	-					288
	gac Asp														336
	ccc Pro													_	384
	cca Pro	-			-			_							432

286

	130					135					140					
				-	cca Pro 150							_	_	-		480
					gaa Glu											528
					cgc Arg			_	-	_		-			-	576
-	-	-			cta Leu			_				-			_	624
				-	aca Thr										-	672
					aca Thr 230											720
			-		atc Ile	_	-					_	-		_	768
	-				gaa Glu				-	-	-	_			٠.	816
				-	tat Tyr		-		-		-			tga *		861

<210> 204

<211> 286

<212> PRT

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<220>

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cag gtg ctc cct gtg ttg aaa gag aat gtg gaa ggt cat gat tta cct 528 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 gca tct gag aaa cac cag gat gtt acc tcc taa 561 Ala Ser Glu Lys His Gln Asp Val Thr Ser * 180 185 <210> 206 <211> 186 <212> PRT <213> Homo sapiens <400> 206 Met Ile His Trp His Ser Glu Lys Ala Thr Leu Leu Leu Asn Ala Pro 10 Ser Phe Ser Asp Gln Leu Pro Gly Thr Met Ala Thr Leu Ser Leu Val 25 Asn Glu Ala Gln Tyr Leu Leu Ile Asn Thr Ser Ser Ile Leu Glu Leu His Arg Gln Leu Asn Thr Ser Asp Glu Asn Gly Lys Glu Glu Leu Phe Ser Leu Lys Asp Leu Ser Leu Arg Phe Arg Ala Asn Ile Ile Asn 70 Gly Lys Arg Ala Phe Glu Glu Glu Lys Trp Asp Glu Ile Ser Ile Gly Ser Leu Arg Phe Gln Val Leu Gly Pro Cys His Arg Cys Gln Met Ile 105 Cys Ile Asp Gln Gln Thr Gly Gln Arg Asn Gln His Val Phe Gln Lys 120 Leu Ser Glu Ser Arg Glu Thr Lys Val Asn Phe Gly Met Tyr Leu Met 130 135 140 His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser 150 155 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 170 165 Ala Ser Glu Lys His Gln Asp Val Thr Ser 180 185 <210> 207 <211> 1272 <212> DNA

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	gtt Val													-	-	96	
	tca Ser												_	-	-	144	
_	gaa G1u 50			_		_			-	-	_	-	_			192	
	cag G1n				-								_			240	
	agt Šer						-			_	-	-			-	288	
	tac Tyr															336	
	caa Gln			-				-			_		-	-		384	
	cca Pro					_	-	-	_	_				_		432	

	130					135					140						
_		-			cac His 150	-			-						-		480
			_		cat His						_				-		528
					atc Ile												576
	-		_		gct Ala	-	-				_	-					624
					gaa Glu												672
		_			caa G1n 230						-		_	Met			720
					att Ile	-									-		768
	-	-			ttc Phe	•				_	-						816
					gta Val							_				•	864
					tta Leu		_										912
				_	cct Pro			_					-	-			960

305	310	315	320
Thr Trp Ile Val T		agt tac aca gtt gtg Ser Tyr Thr Val Val 330	
-		acg ttt tac agc tcc Thr Phe Tyr Ser Ser 350	* *
		gta tta ttg ttg ttg Val Leu Leu Leu Leu 365	
		cat gaa aac att cag His Glu Asn Ile Gln 380	
		aat tot ttg gga cag Asn Ser Leu Gly Gln 395	-
Phe Ser Thr Thr A	• •	cag aat caa gaa ata Gln Asn Gln Glu Ile 410	-
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Phe	Ser	G1y 35	Pro	Met	Met	Ile	11e 40	Thr	Gln	Lys	Ile	Thr 45	Ser	Leu	Ala
Cys	G1u 50	Ile	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	Glu 60	Glu	Leu	Thr	Ser
Ser 65	Gln	Arg	Asp	Leu	Ala 70	Val	Arg	Arg	Met	Pro 75	Ser	Leu	Leu	Glu	Tyr 80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	Ile 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
Ser	Tyr	Lys	Asp 100	Tyr	He	Thr	Phe	Ile 105	Glu	Gly	Arg	Ser	Tyr 110	His	Ile
Thr	Gln	Ser 115	Gly	Glu	Asn	Gly	Lys 120	Glu	Glu	Thr	Gln	Tyr 125	Glu	Arg	Thr
G1u	Pro 130	Ser	Pro	Asn	Thr	Ala 135	Val	Val	Gln	Lys	Leu 140	Leu	Val	Cys	Gly
145					His 150					155					160
Tyr	Asn	Пe	Asp	G1u 165	His	Phe	Gln	Ala	Thr 170	Ala	Ser	Trp	Pro	Thr 175	Lys
		•	180	•	Ile			185			_		190		_
Phe	Ala	Trp 195	Thr	Leu	Ala	Asp	Ala 200	Ile	Asn	Asn	Ala	Ala 205	Gly	Phe	Gly
Phe	Arg 210	Gly	Tyr	Asp	Glu	Asn 215	Gly	Ala	Ala	Arg	Trp 220	Asp	Leu	Ile	Ser
Asn 225	Leu	Arg	Ile	Gln	G1n 230	Ile	Glu	Met	Ser	Thr 235	Ser	Phe	Lys	Met	Phe 240
Leu	Asp	Asn	Trp	Asn 245	Ile	Gln	Thr	Ala	Leu 250	Trp	Leu	Lys	Arg	Val 255	Cys
Tyr	Glu	Arg	Thr 260	Ser	Phe	Ser	Pro	Thr 265	Ile	Gln	Thr	Phe	Ile 270	Leu	Ser
Ala	He	Trp 275		Gly	Val	Tyr		Gly		Tyr	Leu	Thr 285	Phe	Leu	Thr
Gly	Va1 290	Leu	Met	Thr	Leu	A1a 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn.	Phe	Arg
His 305	Tyr	Phe	Пе	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	۷al	Ile 320
Thr	Trp	Пe	Val	Thr 325	G1n	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340	Пe	Lys	Pro	Ser	Leu 345	Thr	Phe	Tyr	Ser	Ser 350	Trp	Tyr
Tyr	Cys	Leu 355	His	Ile	Leu	Gly	Ile 360	Leu	Val	Leu	Leu	Leu 365	Leu	Pro	Val

Lys	Lys 370	Thr	Gln	Arg	Arg	Lys 375	Asn	Thr	His	Glu	Asn 380	He	Gln	Leu	Ser	
G1n 385	Ser	Lys	Lys	Phe	Asp 390	Glu	Gly	Glu	Asn	Ser 395	Leu	Gly	Gln	Asn	Ser 400	
Phe	Ser	Thr	Thr	Asn 405	Asn	Val	Cys	Asn	G1n 410	Asn	Gln	Glu	Пе	Ala 415		
Arg	His	Ser	Ser 420	Leu	Lys	Gln										
		212>	1413 DNA	3 o sap	oiens	S										
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ata		400>		gga	acc	cta	aat:	aat	acc	cat	acc	aaa	cta	GG 3	cto	48
				Gly 5												40
				gcc Ala	-			-		-					_	96
				cgg Arg		_	_			-	_	_	_	_		144
		Leu		tat Tyr			Thr	Ser	Asp		Gly				-	192
				gtc Val												240
				gaa Glu 85												288
gtg	ctg	acc	agc	ctt	gtg	gcg	ctg	cgg	cgg	gag	gtg	gag	gag	ctg	aga	336

Val	Leu	Thr	Ser 100	Leu	Val	Ala	Leu	Arg 105	Arg	Glu	Val	Glu	Glu 110	Leu	Arg	
-			-			gcg Ala							_	-	_	384
						aga Arg 135										432
-				_	_	tcc Ser				-		-			_	480
_		-		-	_	ttc Phe		-	_		-	-				528
						tct Ser	-								_	576
						gaa Glu										624
						ttg Leu 215										672
_	_	_		_		ggt Gly				_		-		_		720
						gag Glu										768
				_	_	ctg Leu				_					-	816
cgg	cag	gac	ttt	ctc	tgg	cgc	ctg	gcc	cga	gcc	tac	agt	gac	atg	tgt	864

Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys	
	ctc Leu 290				-									-		912
	gaa Glu					-								_	-	960
_	cac His	-			-			-		_	_	_			Glu	1008
	atc Ile															1056
_	aaa Lys	_		_		_		-				-				1104
	ggc Gly 370			-		-	-			_	_			-		1152
	act Thr	-		-	_		-	_			-	-			_	1200
-	gcc Ala		_	-			-	_	_			_				1248
	aaa Lys	-			-				_	_		_				1296
	aac Asn															1344
gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

297

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Leu	Leu	Gln	Gln	A1a 245	Asp	Glu	Leu	His	Arg 250	Gly	Asp	Glu	Gln	G1y 255	Lys		
Arg	Glu	Gly	Phe 260	Gln	Leu	Leu	Leu	Asn 265		Lys	Leu	Val	Tyr 270		Ser		
Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285		Met	Cys		
Glu	Leu 290	Thr	Glu	Glu	Val	Ser 295	Glu	Lys	Lys	Ser	Tyr 300	Ala	Leu	Asp	Gly		
Lys 305	Glu	Glu	Ala	Glu	Ala 310	Аlа	Leu	Glu	Lys	Gly 315	Asp	Glu	Ser	Ala	Asp 320		
Cys	His	Leu	Trp	Tyr 325	Ala	Val	Leu	Cys	Gly 330	Gln	Leu	Ala	Glu	His 335	Glu		
Ser	Ile	Gln	Arg 340	Arg	Ile	Gln	Ser	Gly 345	Phe	Ser	Phe	Lys	G1u 350	His	Va1		
Asp	Lys	A1a 355	Ile	Ala	Leu	Gln	Pro 360	Glu	Asn	Pro	Met	A1 a 365	His	Phe	Leu		ė
Leu	Gly 370	Arg	Trp	Cys	Tyr	G1n 375	Val	Ser	His	Leu	Ser 380	Trp	Leu	Glu	Lys		
Lys 385	Thr	Ala	Thr	Ala	Leu _. 390	Leu	Glu	Ser	Pro	Leu 395	Ser	Ala	Thr	Val	G1u 400	-	•
Asp	Ala	Leu	Gln	Ser 405	Phe	Leu	Lys		Glu 410	Glu	Leu	Gln	Pro	Gly 415	Phe		
Ser	Lys	Ala	Gly 420	Arg	Val	Tyr	Ile	Ser 425	Lys	Cys	Tyr	Arg	G1u 430	Leu	Gly		
	Asn	435				,	440					445					
	Va1 450					Leu 455	Ala	Ile	Gln	Lys	Asp 460	Leu	Glu	Glu	Leu		
G1u 465	Val	Ile	Leu	Arg	Asp 470									•			
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				att Ile											
				ctc Leu						-				_	144
	-	_	_	tcc Ser		-			-	_	_		_	_	192
_	 		_	ggc Gly 70	_	-	-				-	-	_	-	240
				999 Gly	_	-					-				-288
	-		-	ttt Phe	_	-			-			-	-		336
				tcc Ser									-		384
				tgg Trp	_					-	-	-		_	432
				cag Gln 150	_	-	_	_	_	_		-	_	_	480
				ccc Pro	_	_				_			-		528
				gag Glu											576

		_		_		_	ctc Leu 200	_				_		_		624
-			_				agg Arg	_	_	-		-	-		•	672
							ttc Phe				-				_	720
-		-				_	aaa Lys			_	-	_		•		768
					-		cct Pro					Glu	-	_	•	816
			_			-	gag Glu 280	_	-	-		-				864
				•			gag Glu	_		-					-	912
							ctg Leu			-		-			tac Tyr 320	960
							agc Ser	Met								1008
			_				gtc Val				_				_	1056
	Trp						gaa Glu 360		-	-			-			1104

301

aac tot gac agc aag cag aaa otg aat gac tga 1137 Asn Ser Asp Ser Lys Gln Lys Leu Asn Asp * 370 375 <210> 212 <211> 378 <212> PRT <213> Homo sapiens <400> 212 Met Asp Leu Ala Gly Leu Leu Lys Ser Gln Phe Leu Cys His Leu Val 5 Phe Cys Tyr Val Phe Ile Ala Ser Gly Leu Ile Ile Asn Thr Ile Gln 25 Leu Phe Thr Leu Leu Leu Trp Pro Ile Asn Lys Gln Leu Phe Arg Lys Ile Asn Cys Arg Leu Ser Tyr Cys Ile Ser Ser Gln Leu Val Met Leu 55 Leu Glu Trp Trp Ser Gly Thr Glu Cys Thr Ile Phe Thr Asp Pro Arg 70 Ala Tyr Leu Lys Tyr Gly Lys Glu Asn Ala Ile Val Val Leu Asn His 90 Lys Phe Glu Ile Asp Phe Leu Cys Gly Trp Ser Leu Ser Glu Arg Phe 105 Gly Leu Leu Gly Gly Ser Lys Val Leu Ala Lys Lys Glu Leu Ala Tyr 120 Val Pro Ile Ile Gly Trp Met Trp Tyr Phe Thr Glu Met Val Phe Cys Ser Arg Lys Trp Glu Gln Asp Arg Lys Thr Val Ala Thr Ser Leu Gln 150 155 His Leu Arg Asp Tyr Pro Glu Lys Tyr Phe Phe Leu Ile His Cys Glu 165 170 Gly Thr Arg Phe Thr Glu Lys Lys His Glu Ile Ser Met Gln Val Ala 180 185 Arg Ala Lys Gly Leu Pro Arg Leu Lys His His Leu Leu Pro Arg Thr 200 Lys Gly Phe Ala Ile Thr Val Arg Ser Leu Arg Asn Val Val Ser Ala 215 220 Val Tyr Asp Cys Thr Leu Asn Phe Arg Asn Asn Glu Asn Pro Thr Leu 230 235 Leu Gly Val Leu Asn Gly Lys Lys Tyr His Ala Asp Leu Tyr Val Arg 245 250

WO 01/29221

Arg	Ile	Pro	Leu 260	Glu	Asp	Ile	Pro	G1u 265	Asp	Asp	Asp	Glu	Cys 270	Ser	Ala	
Trp	Leu	His 275	Lys	Leu	Tyr	Gln	G1u 280	Lys	Asp	Ala	Phe	G1n 285	Glu	Glu	Tyr	
Tyr	Arg 290	Thr	Gly	Thr	Phe	Pro 295	Glu	Thr	Pro	Met	Val 300	Pro	Pro	Arg	Arg	
Pro 305	Trp	Thr	Leu	Val	Asn 310		Leu	Phe	Trp	Ala 315		Leu	Val	Leu	Tyr 320	
	Phe	Phe	Gln	Phe 325		۷a٦	Ser	Met	Ile 330		Ser	Gly	Ser	Ser 335		
Thr	Leu	Ala	Ser 340		Ile	Leu	Val	Phe 345		Val	Ala	Ser	Val 350		Val	
Arg	Trp	Met 355		Gly	Val	Thr	G1u 360		Asp	Lys	Gly	Ser 365		Tyr	Gly	
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	gcg Ala								-							144
_	acc Thr 50					-					_	_	-	-		192
ССС	agc	aac	acc	cct	gcc	acg	ccg	ССС	aac	ttc	ССС	gat	gcg	ctg	gcc	240

Pro 65	Ser	Asn	Thr	Pro	Ala 70	Thr	Pro	Pro	Asn	Phe 75	Pro	Asp	Ala	Leu	Ala 80	
_			-		cgc Arg	-				_	_	_	-		_	288
	_		_	_	gcc Ala	_				-			_			336
		_		-	ccc Pro								_			384
					cac His						_		_			432
		_	_	_	999 Gly 150		-	-	_		-	_		-	_	480
-	ggc Gly	_	aga Arg	tga *												495
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1				5	Gly			_	10					15		
•			20		Gln			25					30			
		35		•	,	•	40					45				
	50				Asn	55					60			·		
Pro 65	Ser	Asn	Thr	Pro	Ala 70	Thr	Pro	Pro	Asn	Phe 75	Pro	Asp	Ala	Leu	Ala 80	

Met	Phe	Ser	Lys	Leu 85	Arg	Ala	Ser	Glu	Gly 90	Leu	Gln	Ser	Ser	Asn 95	Ser		
Pro	Met	Thr	Ala 100	Ala	Ala	Cys	Ser	Pro 105	Pro	Ala	Asn	Phe	Ser 110	Pro	Phe		
Trp	Ala	Ser 115	Ser	Pro	Pro	Ser	His 120	Gln	Ala	Pro	Trp	Ile 125	Pro	Pro	Ser		
Ser	Pro 130	Thr	Thr	Phe	His	His 135	Leu	His	Arg	Pro	Gln 140	Pro	Thr	Trp	Pro	.*	
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	_			_			_	_		_		_	_	aag Lys			96
-	Leu	Lys	Arg	Arg	Asn		Āsp	Ile	Thr	Gly	-	Lys	Thr	gtg Val			144
														cca Pro			192
														cca Pro			240
222	aac	222	aat	222	222	cat	naa	ac a	nat	กลด	tta	ant	aa s	nat	act		288

Lys	Gly	Lys	Gly	Lys 85	Lys	His	Glu	Ala	Asp 90	Glu	Leu	Ser	Gly	Asp 95	Ala	
				gat Asp	-			_	-	_	-	-				336
			Glu	caa Gln	-			-	_		_	-		_	•	384
				gaa Glu												432
				aag Lys												480
				aaa Lys 165					-		-		_	_		528
		-		gat Asp					_		-			•	gaa Glu	576
				gat Asp												624
				cct Pro		-				-	-	_	-			672
				atg Met												720
				gtc Val 245			_	_	-	_	_			-	•	768
tt	gat	ggt	gat	gac	ctc	cta	gaa	aca	ggt	aaa	aat	qtq	aaa	att	aca	816

Phe	Asp	Gly	Asp 260	Asp	Leu	Leu	Glu	Thr 265	Gly	Lys	Asn	Val	Lys 270	Île	Thr	
_	•	-	-	-	_			-		_	-	-	att Ile	-	_	864
-	_				-	-	-						aac Asn			912
-		-	-	_	-	-		_		-		_	gag Glu	_	-	960
_	_	-	_		_		-	-			_		gaa Glu	_	_	1008
	-	_				_				-			caa G1n 350	_	-	1056
-			-	-			_	-	_				aaa Lys	_	-	1104
													tca Ser			1152
			-	-								-	gct Ala	•	•	1200
													aaa Lys		-	1248
							_		-				gta Val 430		_	1296
tct	tca	agc	aca	gag	gtg	tcc	agg	tgt	att	gca	cat	ctt	cat	cgc	act	1344

Ser	Ser	Ser 435	Thr	Glu	Vaì	Ser	Arg 440	Cys	IJе	Ala	His	Leu 445	His	Arg	Thr	
	-			-	_	att Ile 455								_		1392
	_		-	-	-	aaa Lys	-		- ,		-		_		-	1440
-			-			aat Asn	_	_	-	-	-	-	-			1488
-		-			_	gag Glu		_						_		1536
	-	-	_	_		aag Lys			-			-		_		1584
-				-		caa Gln 535			-	-				-	-	1632
-	_	-	-		-	tcc Ser	_	_				_	-			1680
-					-	cat His	_	_				-		_		1728
					-	agt Ser	_	_	_		_	_	_		-	1776
						tac Tyr										1824
aag	atg	aag	gaa	саа	agg	ttg	aga	gaa	cat	tta	gtt	cgt	ttt	gaa	agg	1872

Lys	Met 610	Lys	Glu	Gln	Arg	Leu 615	Arg	Glu	His	Leu	Va1 620	Arg	Phe	Glu	Arg	
	cga Arg			_	_										_	1920
	cgt Arg	-		-	Ğlu	-		_			-	-		_	_	1968
	gaa Glu	-		_	-		-						_			2016
	cta Leu	-	-		-	_	-	Arg						-	_	2064
	cgt Arg 690		-	-	-	_	_	_	_	_	-			-	-	2112
	aga Arg				_											2160
_	aaa Lys						_		_	-	-	-			_	2208
	gat Asp															2256
-	cga Arg						-			-		-		-		2304
	gac Asp 770															2352
gta	cag	tct	tca	tct	ttt	gaa	agg	cgg	gat	cgc	ttt	gtt	ggt	caa	agt	2400

Va1 785	Gln	Ser	Ser	Ser	Phe 790	Glu	Arg	Arg	Asp	Arg 795	Phe	Val	Gly	Gln	Ser 800	
				-	cga Arg				-					-		2448
-	-				aat Asn		-	_		-	-					2496
		_		-	ctt Leu	-	_				-	-	-	-		2544
	-	_	_		aga Arg	-					-			_		2592
			_		cct Pro 870	_	_							-		2640
				_	gaa Glu		_	-			_			-		2688
					gaa Glu										-	2736
	-		_		cct Pro			-	_	-	-	-				2784
-	-			_	aga Arg		-			-	_					2832
_					gag G1u 950	-			-	-	_				_	2880
aca	agc	gga	cca	agg	aaa	gag	tgg	cat	ggt	cca	ссс	tct	caa	ggg	cct	2928

								•								
Thr	Ser	Gly	Pro	Arg 965	Lys	Glu	Trp	His	Gly 970	Pro	Pro	Ser	Gln	Gly 975	Pro	
		• •	gat Asp 980	_										_		2976
_			caa Gln			_		Ala					Arg		-	3024
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	Phe	-	ggt Gly			Pro	-	-		tga *						3105
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Glu	Leu	Lys 35	Arg	Arg	Asn	Leu	Asp 40		Thr	Gly	Val	Lys 45		۷a٦	Leu	
Пе	Ser 50		Leu	Lys	Gln	Ala 55		Glu	Glu	Glu	Gly 60		Asp	Pro	Asp	
Asn 65	-	Glu	Leu	Thr	Val 70	-	Thr	Asp	Thr	Pro 75		Lys	Ļys	Pro	Thr 80	
	Gly	Lys	Gly	Lys 85		His	Glu	Ala	Asp 90		Leu	Ser	Gly	`		
Ser	۷al	Glu	Asp 100		Ala	Phe	Пе	Lys 105		Cys	Glu	Leu	Glu 110	95 Asn	Gln	
Glu	Ala	His 115	Glu	Gln	Asp	Gly	Asn 120		Glu	Leu	Lys	Asp 125		Glu	Glu	
DI.	01.	01.	A .	Λ1	01	01	14.0			C -		220			_	

Phe Gly Glu Asn Glu Glu Glu Asn Val His Ser Lys Glu Leu Leu Ser

140

135

	Glu	Glu	Asn	Lys	_	Ala	His	Glu	Leu		Glu	Ala	Glu	Gly	
145					150			0.3	_	155		-:	0.7		160
Glu	Asp	He	Glu	Lys 165	Glu	Asp	He	Glu	Ser 170	GIn	Glu	He	Glu	A1a 175	Gln
Glu	Gly	Glu	Asp 180	Asp	Thr	Phe	Leu	Thr 185	Ala	Gln	Asp	Gly	Glu 190	Glu	Glu
Glu	Asn	G1u 195		Asp	Ile	Ala	Gly 200	Ser	Gly	Asp	Gly	Thr 205	Gln	Glu	Val
Ser	Lys 210	Pro	Leu	Pro	Ser	G1u 215	Gly	Ser	Leu	Ala	G1u 220	Ala	Asp	His	Thr
Ala 225	His	Glu	Glu	Met	G1u 230	Alà	His	Thr	Thr	Val 235	Lys	Glu	Ala	Glu	Asp 240
	Asn	Ile	Ser	Va1 245		Ile	Gln	Ala	G1u 250		Ala	Ile	Thr	Leu 255	
Phe	Asp	Gly	Asp 260		Leu	Leu	Glu	Thr 265		Lys	Asn	Val	Lys 270		Thr
Asp	Ser	G1u 275		Ser	Lys	Pro	Lys 280		Gly	Gln	Asp	A1a 285		Ala	Gln
Ser	Pro		Lys	Glu	Ser	Lys 295		Tyr	Glu	Met	Asn 300		Asn	His	Lys
Asp	290 Gly	Lys	Lys	Glu	Asp		Val	Lys	Gly	Asp		Val	Glu	Lys	Glu
305					310					315					320
Ala	Arg	Glu	Ser	Ser 325	Lys	Lys	Ala	Glu	Ser 330	Gly	Asp	Lys	Glu	Lys 335	Asp
Thr	Leu	Lys	Lys 340	Gly	Pro	Ser	Ser	Thr 345	Gly	Ala	Ser	Gly	G1n 350	Ala	Lys
Ser	Ser	Ser 355	Lys	Glu	Ser	Lys	Asp 360	Ser	Lys	Thr	Ser	Ser 365	Lys	Asp	Asp
Lys	G1 <i>y</i> 370	Ser	Thr	Ser	Ser	Thr 375	Ser	Gly	Ser	Ser	G1y 380	Ser	Ser	Thr	Lys
. Asn 385	Ile	Trp	Val	Ser	G1 <i>y</i> 390	Leu	Ser	Ser	Asn	Thr 395	Lys	Ala	Ala	Asp	Leu 400
Lys	Asn	Leu	Phe	Gly 405	Lys	Tyr	Gly	Lys	Val 410	Leu	Ser	Ala	Lys	Val 415	Val
Thr	Asn	Ala	Arg 420	Ser	Pro	Gly	Ala	Lys 425	Cys	Tyr	Gly	Ile	Val 430	Thr	Met
Ser	Ser	Ser 435		Glu	Val	Ser	Arg 440		Пе	Ala	His	Leu 445		Arg	Thr
Glu	Leu 450		Gly	Gln	Leu	Ile 455		Val	Glu	Lys	Va1 460		Gly	Asp	Pro
Ser 465	Lys	Lys	Glu	Met	Lys 470		Glu	Asn	Asp	G1u 475		Ser	Ser	Ser	Arg 480
	Ser	Gly	Asp	Lys 485		Asn	Thr	Ser	Asp 490		Ser	Ser	Lys	Thr 495	

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Lys	Glu	Ser 515	Lys	Asp	Thr	Lys	Lys 520	Ile	Glu	Gly	Lys	Asp 525	Glu	Lys	Asn
Asp	Asn 530	Gly	Ala	Ser	Gly	G1n 535	Thr	Ser	G1u	Ser	11e 540	Lys	Lys	Ser	Glu
G1u 545	Lys	Lys	Arg	Ile	Ser 550		Lys	Ser	Pro	Gly 555	His	Met	Val	Пе	Leu 560
	Gln	Thr	Lys	Gly 565		His	Cys	Arg	Pro 570		Arg	Arg	Gly	Arg 575	
Glu	Lys	Ile	His 580		Arg	Ser	Lys	G1u 585		Glu	Arg	Ala	Ser 590		Asp
Lys	Lys	Arg 595		L.ys	Asp	Tyr	Arg 600		Lys	Glu	Ile	Leu 605		Phe	Glu
Lys	Met 610			Gln	Arg	Leu 615		Glu	His	Leu	Va1 620		Phe	Glu	Arg
Leu 625	Arg	Arg			G1u 630		Arg	Arg	Arg	Arg 635		Ile	Ala	Glu	Arg 640
	Arg	Arg	G1u	Arg 645		Arg	Пe	Arg	11e 650		Arg	Glu	Arg	G1u 655	
Arg	Glu	Arg	Leu 660		Arg	Glu	Arg	G1u 665		Leu	Glu	He	G1u 670		Gln
Lys	Leu	G1u 675		Glu	Arg	Met	G1u 680		Glu	Arg	Leu	G1u 685	Arg	Glu	Arg
Ile	Arg 690		G1u	Gln	G1u	Arg 695		Lys	Glu	Ala	G1u 700			Ala	Arg
G1u 705	Arg	Glu	Glu	Leu	Arg 710		Gln	Gln	Gln	Gln 715		Arg	Tyr	Glu	G1n 720
	Lys	Arg	Asn	Ser 725		Lys	Arg	Pro	Arg 730		Val	Asp	His	Arg 735	
Asp	Asp	Pro	Tyr 740		Ser	Glu	Asn	Lys 745		Leu	Ser	Leu	Asp 750		Asp
Ą٦a	Arg	Phe 755		His	Gly	Ser	Asp 760		Ser	Arg	Gln	G1n 765		Arg	Phe
Asn	Asp 770		Asp	His	Arg	G1u 775		Gly	Arg	Phe	Pro 780		Ser	Ser	Ala
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Glu	Arg	Tyr	Pro 820		Asn	Phe	Ser	Asp 825		Arg	Arg	Asn	G1u 830		Pro
Pro	Pro	Arg 835		Glu	Leu	Arg	G1u 840		Asp	Arg	Arg	G1u 845		Arg	Gly

Glu Arg Asp Glu Arg Arg Thr Val Ile Ile His Asp Arg Pro Asp Ile 855 860 Thr His Pro Arg His Pro Arg Glu Ala Gly Pro Asn Pro Ser Arg Pro 865 870 Thr Ser Trp Lys Ser Glu Gly Ser Met Ser Thr Asp Lys Arg Glu Thr 885 890 Arg Val Glu Arg Pro Glu Arg Ser Gly Arg Glu Val Ser Gly His Ser 905 Val Arg Gly Ala Pro Pro Gly Asn Arg Ser Ser Ala Ser Gly Tyr Gly 920 925 Ser Arg Glu Gly Asp Arg Gly Val Ile Thr Asp Arg Gly Gly Gly Ser 935 940 Gln His Tyr Pro Glu Glu Arg His Val Val Glu Arg His Gly Arg Asp 950 955 Thr Ser Gly Pro Arg Lys Glu Trp His Gly Pro Pro Ser Gln Gly Pro 965 970 Ser Tyr His Asp Thr Arg Arg Met Gly Asp Gly Arg Ala Gly Ala Gly 985 Met Ile Thr Gln His Ser Ser Asn Ala Ser Pro Ile Asn Arg Ile Val 1000 1005 Gln Ile Ser Gly Asn Ser Met Pro Arg Gly Ser Gly Ser Gly Phe Lys 1010 1015 1020 Pro Phe Lys Gly Gly Pro Pro Arg Arg Phe 1025 1030 <210> 217 <211> 1428 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1428) <400> 217 48 atg cct cac agg aag aaa aag ccc ttt ata gag aag aag aaa gct gtg Met Pro His Arg Lys Lys Lys Pro Phe Ile Glu Lys Lys Lys Ala Val 10 tct ttt cac ttg gtc cac cgg agc caa cga gat cct tta gca gca gat 96 Ser Phe His Leu Val His Arg Ser Gln Arg Asp Pro Leu Ala Ala Asp 20 25 30

gag agt gca ccc cag agg gtt cta ttg ccc aca caa aaa ata gac aat

Glu	Ser	A1a 35	Pro	Gln	Arg	Val	Leu 40	Leu	Pro	Thr	Gln	Lys 45	Ile	Asp	Asn		
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_		-		_	_		-	_	-					tca Ser			240
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•	-	_		-			-				_	-		tca Ser			336
		-		_			_	-	_		-			aaa Lys	-		384
-		-				-	_	-		-		-		gtt Val	-		432
-		-	-	-		-		-	-		-		_	ctt Leu			480
gat Asp														gag Glu 175			528
-	-		_					-	-	-	-			gaa Glu	-	-	576
	_	-		-		_	-		-	_		-		gca Ala			624
cta	ttg	tca	gat	gaa	gac	tgt	atg	tct	gtg	ссс	gga	aaa	act	cac	aga		672

Leu	Leu 210	Ser	Asp	Glu	Asp	Cys 215	Met	Ser	Val	Pro	Gly 220	Lys	Thr	His	Arg	
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_			•	_				-	-		-		-	cag Gln 255	-	768
			-	-										gat Asp		816
_	_			_	_	-			-					att Ile		864
	_	-		_		_	_							aaa Lys		912
_	-			-	-		_						-	gag Glu	_	960
	-	-		_				-					-	gaa Glu 335	_	1008
		-	_		•	_	-			-		-	-	gaa Glu		1056
	_	-										_		atc Ile	_	1104
			•					-						gga Gly		1152
cct	ctc	aat	gtc	tta	cca	aag	aaa	gga	ctc	aca	gca	aag	caa	act	gaa	1200

Pro 385	Leu	Asn	Val	Leu	Pro 390	Lys	Lys	Gly	Leu	Thr 395	Ala	Lys	Gln	Thr	G1u 400	
_	ata Ile	_	-				-	-				-			_	1248
	cgt Arg													-		1296
-	ata Ile		-		-	_	-		-			•		-		1344
	tta Leu 450				_						_			_	-	1392
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Ser	Phe	His	Leu 20	Val	His	Arg	Ser	G1n 25	Arg	Asp	Pro _.	Leu	A1a 30	Ala	Asp	
Glu	Ser	A1a 35		Gln	Arg	Val	Leu 40		Pro	Thr	Gln	Lys 45		Asp	Asn	
Glu	G1u 50	Arg	Arg	Ala	Glu	G1n 55	Arg	Lys	Tyr	Gly	Va1 60	Phe	Phe	Asp	Asp	
Asp 65	Tyr	Asp	Tyr	Leu	G1n 70	His	Leu	Lys	Glu	Pro 75		Gly	Pro	Ser	Glu 80	
	Ile	Pro	Ser	Ser 85	Thr	Phe	Ser	Ala	His 90	Asn	Arg	Arg	Glu	Glu 95		
G1u	Glu	Thr	Leu 100	Val	Пe	Pro	Ser	Thr 105		Пe	Lys	Leu	Pro 110		Ser	

vai	Pne	115	ser	GIU	Pne	GIU	120	ASP	vai	ыу	Leu	125	Asn	Lys	Ala
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Ala 145	Leu	Asp	Asp	Asp	Phe 150	Asp	Phe	Asp	Asp	Pro 155	Asp	Asn	Leu	Leu	G1u 160
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		_			gtc Val		-			_			-		576
					tac Tyr										624
		-	_	_	aga Arg			_					_		672
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321

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Glu	Glu	He	Glu	Ala	Leu	Ser	мет		rne	ıyr	ser.	ser.	270	GIU	rie
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IJο	Val		G1n	Sar	Lau	Λcn		Thr	Leu	Thr	Ara		Glu	Asn	Thr
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CTV	370	Dro	Leu	د ۲۸	Λ 1 =			Gln	Pro	His		Glv	Ser	Glv	Πe
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Val	Val	Val	Va1 260	Leu	Leu	Leu	Gln	Gly 265	Leu	Ser	Leu	Leu	G1u 270	Leu	Leu-	
Asp	Phe	Pro 275	Pro	Leu	Phe	Trp	Val 280	Leu	Asp	Ala	His	Ala 285	Ile	Trp	His	
He	Ser 290	Thr	Ile	Pro	Val	His 295	Val	Leu	Phe	Phe	Ser 300	Phe	Leu	Glu	Asp	
Asp 305	Şer	Leu	Tyr	Leu	Leu 310	Lys	Glu	Ser	Glu	Asp 315	Lys	Phe	Lys	Leu	Asp 320	
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Met 1 cgc		222> 223> 400> cgg Arg	(1) n = 229 aag Lys	aag Lys 5	557) ,C or gtg	cgt Arg	Pro	Arg ctg	Leu 10 aac	Ile agg	Ala ccg	Xaa cgc	Leu gac	Ala 15 tcc	Arg cag	48 96
Met 1 cgc Arg	<2 gcg Ala gtg Val	222> 223> 400> cgg Arg cgc Arg	(1) n = 229 aag Lys gcc Ala 20 gtg	aag Lys 5 ctg Leu	557) C or gtg Val	cgt Arg gag Glu	Pro caa Gln acc	ctg Leu 25	Leu 10 aac Asn	agg Arg	Ala ccg Pro	Xaa cgc Arg	gac Asp 30	Ala 15 tcc Ser	Arg cag Gln cgc	
Met 1 cgc Arg ctc Leu	<pre></pre> <pre></pre> <pre></pre> <pre></pre> <pre> <pre> <pre>gcg Ala gtg Val tac Tyr ctg </pre></pre></pre>	222> 223> 400> cgg Arg cgc Arg gcg Ala 35	(1) n = 229 aag Lys gcc Ala 20 gtg Val	aag Lys 5 ctg Leu gac Asp	gtg Val cgg Arg	cgt Arg gag Glu gag Glu	Pro caa Gln acc Thr 40 gcc	ctg Leu 25 ttg Leu	Leu 10 aac Asn acg Thr	agg Arg cgg Arg	Ala ccg Pro ccg Pro	xaa cgc Arg ttc Phe 45	gac Asp 30 tct Ser	Ala 15 tcc Ser gga Gly	Arg cag Gln cgc Arg	96

.334

Leu 65	Gln	Leu	Leu	Gly	Arg 70	Leu	Pro	Leu	Phe	G1y 75	Leu	Gly	Arg	Leu	Val 80	
_	-	_			_	tgg Trp	_		_		_	_			_	288
	_					gac Asp		-	-	-		-	-			336
_	_		ĠĨy		_	açc Thr				_			-			384
	-					atg Met 135									-	432
				-		acc Thr			-	-		-	_	-	-	480
_	_			_		ccg Pro					_	_			_	528
_	_	_				gac Asp		_					_	_		576
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Arg Leu Pro Val Arg Ala Trp Ala Asp Val Arg Arg Glu Xaa Arg Leu
Leu Gln Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
                    70
                                        75
Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
                                    90
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
            100
                                105
Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
                            120
Arg Glu Ile Glu His Val Met Tyr His Asp Trp Arg Leu Val Pro Lys
                        135
                                            140
His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
                    150
                                        155
Leu Ala Ser Val Pro Tyr Pro Pro Leu Leu Arg Ala Met Ile Ile Ala
                                    170
Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
                               185
Val Gln Arg Ile Arg Met Glu Pro Trp Asp Tyr Pro Ala Lys Gln Glu
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Asp Lys Gly Arg Ala Lys Gly Thr Pro Val
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cca gca gtg aca gac Pro Ala Val Thr Asp 165	Asn Asp Glu Ala A	sp Lys Lys Ala Gly	
aca gag ggc cat tgt Thr Glu Gly His Cys 180			
aag ccc gtc acc tgc Lys Pro Val Thr Cys 195			
gat gcg gac att cac Asp Ala Asp Ile His 210			•
ctg ctc cac ggg cta Leu Leu His Gly Leu 225			•
agg ctg aag gtg tac Arg Leu Lys Val Tyr 245	Lys Leu Lys His Ly	ys His Gly Leu Val	
gcg atg gat gac tac Ala Met Asp Asp Tyr 260			
acc aac atc cag ctc Thr Asn Ile Gln Leu 275	• •		
gaa ctg ggc atc atc Glu Leu Gly Ile Ile 290		-	
atc cac atc cca ggt Ile His Ile Pro Gly 305			_
ccc gcc ctc aag aag Pro Ala Leu Lys Lys			

338

325 330 335 cag gag gag agc gcc gag cgg agn agg ccc tca cag cat gtg gtg ctc 1056 Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu 340 345 age ctg act ttc aag cgt tat gtc ttc gac acc cac aag cgc atg gtt 1104 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 360 365 cag tct ccc tga 1116 Gln Ser Pro * 370 <210> 232 <211> 371 <212> PRT <213> Homo sapiens <220> <221> VARIANT · <222> (1)...(371) <223> Xaa = Any Amino Acid <400> 232 Met Ser Val Ala His Cys Phe Ser Ile Lys Gly Gln Gly Thr Val Met 10 Thr Gly Thr Ile Leu Ser Gly Ser Ile Ser Leu Gly Asp Ser Val Glu 25 Ile Pro Ala Leu Lys Val Val Lys Lys Val Lys Ser Met Gln Met Phe 40 His Met Pro Ile Thr Ser Ala Met Gln Gly Asp Arg Leu Gly Ile Cys 55 Val Thr Gln Phe Asp Pro Lys Leu Leu Glu Arg Gly Leu Val Cys Ala 70 75 Pro Glu Ser Leu His Thr Val His Ala Ala Leu Ile Ser Val Glu Lys Ile Pro Tyr Phe Arg Gly Pro Leu Gln Thr Lys Ala Lys Phe His Ile 105 Thr Val Gly His Glu Thr Val Met Gly Arg Leu Met Phe Phe Ser Pro 120 125 Ala Pro Asp Asn Phe Asp Gln Glu Pro Ile Leu Asp Ser Phe Asn Phe 130 135 140

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Ser Gln Glu Tyr Leu Phe Gln Glu Gln Tyr Leu Ser Lys Asp Leu Thr
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Pro Ala Val Thr Asp Asn Asp Glu Ala Asp Lys Lys Ala Gly Gln Ala
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Thr Glu Gly His Cys Pro Arg Gln Gln Trp Ala Leu Val Glu Phe Glu
                                185
Lys Pro Val Thr Cys Pro Arg Leu Cys Leu Val Ile Gly Ser Arg Leu
                            200
                                                205
Asp Ala Asp Ile His Thr Asn Thr Cys Arg Leu Ala Phe His Gly Ile
                        215
                                            220
Leu Leu His Gly Leu Glu Asp Arg Asn Tyr Ala Asp Ser Phe Leu Pro
                    230
                                        235
Arg Leu Lys Val Tyr Lys Leu Lys His Lys His Gly Leu Val Glu Arg
                245
                                    250
Ala Met Asp Asp Tyr Ser Val Ile Gly Arg Ser Leu Phe Lys Lys Glu
                                265
Thr Asn Ile Gln Leu Phe Val Gly Leu Lys Val His Leu Ser Thr Gly
                            280
Glu Leu Gly Ile Ile Asp Ser Ala Phe Gly Gln Ser Gly Lys Phe Lys
                        295
                                            300
Ile His Ile Pro Gly Gly Leu Ser Pro Glu Ser Lys Lys Ile Leu Thr
305
                    310
                                        315
                                                            320
Pro Ala Leu Lys Lys Arg Ala Arg Ala Gly Arg Gly Glu Ala Thr Arg
                                    330
                325
Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu
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Gln Ser Pro
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										ctg Leu		192
				_		-	_			ggt Gly		240
		-								att Ile		288
-			-			-	_	-		aat Asn		336
-		_	_		_			_		att Ile 125	_	384
		-				_				gaa Glu		432
-	-							-		aag Lys		480
										gga Gly		528

		-	ttt Phe 180									-	_			576
-			gag Glu	-												624
		Ser	act Thr			-	_		-		_					672
	_	•	ctt Leu	_			-						-			720
-			aat Asn		-			-	_				-		~ ~	768
	_		ctt Leu 260							_	-	Ile	-	-	-	816
			ggc Gly													864
			ctg Leu	-												912
		_	atc Ile	_			_								-	960
	_	-	gta Val	-		-	_							_	_	1008
			ttg Leu 340			-									_	1056

	cct Pro															1104
	gct Ala 370															1152
	cct Pro															1200
	gca Ala															1248
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Ala	Val	Ala	Thr 20	Ala	Xaa	Lys	Ser	Asn 25	۷a۱	Thr	Ser	Phe	G1n 30	Arg	Arg	
Gly	Pro	Arg 35		Ser	۷a٦	Thr	Asn 40		Ser	Gly	Pro	Arg 45		Val	Ser	
Ile	A1a 50		Thr	Arg	Pro	Ser 55		Arg	Asn	Gly	G]n 60		Leu	Val	Ser	
Thr 65	Gly	Leu	Pro	Ala	Leu 70		Gln	Leu	Leu	Gly 75		Gly	Leu	A1a	Va1 80	
	Thr	Val	Leu	Leu		Glu	Glu	Asp	Lys		Asn	Ile	Tyr	Ser		

				85					90					95	
Leu	Leu	Phe	Lys 100		Phe	Leu	Ala	Glu 105		Ile	Val	Asn	Gly 110		Thr
Leu	Leu	Val 115		Ser	Ala	Lys	Glu 120		Pro	Ala	Asn	Ile 125	_	Gln	Glu
Leu	Pro 130		Pro	Leu	Leu	Asp 135		Lys	Cys	Lys	Lys 140	Glu	Phe	Asp	Glu
Asp 145		Tyr	Asn	His	Lys 150		Pro	Glu	Ser	Asn 155		Lys	Met	Lys	Ile 160
	Trp	Arg	Tyr	G1n 165		Leu	Pro	Lys	Met 170		Ile	Gly	Pro	Val 175	
Ser	Ser	Arg	Phe 180		His	Tyr	Tyr	Asp 185	Ala	Ser	Lys	Arg	Met 190		Gln
Glu	Leu	Ile 195	Glu	Ala	Ser	Asn	Trp 200	His	Gly	Phe	Phe	Leu 205	Pro	Glu	Lys
Пe	Ser 210	Ser	Thr	Leu	Lys	Val 215	Glu	Pro	Cys	Ser	Leu 220	Thr	Pro	Gly	Tyr
Thr 225	Lys	Leu	Leu	Gln	Phe 230	Пe	Gln	Asn	Пe	Ile 235	Tyr	Glu	Glu	Gly	Phe 240
Asp	Gly	Ser	Asn	Pro 245	Gln	Lys	Lys	Gln	Arg 250	Asn	Ile	Leu	Arg	Ile 255	Gly
He	Gln	Asn	Leu 260	Gly	Ser	Pro	Leu	Trp 265	Gly	Asp	Asp	Ile	Cys 270	Cys	Ala
Glu	Ásn	Gly 275	Gly	Asn	Ser	His	Ser 280	Leu	Thr	Lys	Phe	Leu 285	Tyr	Val	Leu
Arg	Gly 290	Leu	Leu	Arg	Thr	Ser 295	Leu	Ser	Ala	Cys	Ile 300	Пe	Thr	Met	Pro
Thr 305	His	Leu	Ile	Gln	Asn 310	Lys	Ala	Ile	Ile	Ala 315	Arg	Val	Thr	Thr	Leu 320
Ser	Asp	Val	Val	Val 325	Gly	Leu	Glu	Ser	Phe 330	Ile	Gly	Ser	Glu	Arg 335	Glu
Thr	Asn	Pro	Leu 340	Tyr	Lys	Asp	Tyr	His 345	Gly	Leu	Ile	His	Ile 350	Arg	Gln
Пe	Pro	Arg 355	Leu	Asn	Asn	Leu	11e 360	Cys	Asp	Glu	Ser	Asp 365	Val	Lys	Asp
Leu	A1a 370	Phe	Lys	Leu	Lys	Arg 375	Lys	Leu	Phe	Thr	11e 380	Glu	Arg	Leu	His
Leu 385	Pro	Pro	Asp	Leu	Ser 390	Asp	Thr	Val	Ser	Arg 395	Ser	Ser	Lys	Met	Asp 400
Leu	Ala	Glu	Ser	A1a 405	Lys	Arg	Leu	Gly	Pro 410	Gly	Cys	Gly	Met	Met 415	Ala
Gly	Gly	Lys	Lys 420	His	Leu	Asp	Phe								

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		-			ttt Phe	_	_	-	-					_		96
					cag Gln											144
	-		_		gag Glu	_										192
-				_	gcg Ala 70											240
					cgg Arg											288
			_		cat His	_	_							-		336
-		-		_	aag Lys		_									384
•	-	-			cag Gln	_			-		-		-			432

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305	310	315	320
cgg aag cgc ttc tcc Arg Lys Arg Phe Ser 325		a Asp Tyr Ile Ser	
gag ctg gcc caa gtg Glu Leu Ala Gln Val 340	-		
gcc cag gca gca gct Ala Gln Ala Ala Ala 355	•		-
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met		ASP	Leu	Leu	Gln		ыу	Pro	ASP	Vai	140	PIU	Ser	rne	Leu
A	130	V-1	1	۸	C1	135	A = ==	Tan	۸٦ -	Dho		C1	Dha	110	C1
145					Gln 150					155					160
Met	Ile	Gln	Glu	11e 165	Gln	Gln	Ala	Ala	G1u 170	Arg	Leu	Glu	Arg	Asn 175	Phe
Val	Asp	Ser	Arg 180	Gln	Leu	Lys	Val	Cys 185	Ala	Thr	Çys		Asp 190	Leu	Ser
Val	Ser	Leu 195		Arg	Val	Leu	G1u 200	Met	Thr	Пe	Thr	Leu 205	Val	Pro	Glu
Ile	Phe 210		Asp	Trp	.Thr	Arg 215	Pro	Thr	Ser	Glu	Met 220	Leu	Leu	Arg	Arg
Leu 225		Gln	Leu	Leu	Asn 230		Val		Asn	Arg 235	Val	Thr	Ala	G1u	Arg 240
	Leu	Phe	Asp	Arg 245	Val	Val	Thr	Leu	Arg 250	Leu	Pro	Gly	Leu	G1u 255	Ser
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Leu	Leu 290	Ala	Asp	Pro	Cys	Phe 295	Gln	Leu	Arg	Ser	Ile 300	Cys	Tyr	Leu	Leu
G1y 305		Pro	Glu	Pro	Pro 310	Ala	Pro	Gly	Thr	Ala 315	Leu	Pro	Ala	Pro	Asp 320
Arg	Lys	Arg	Phe	Ser 325	Leu	Gln	Ser	Tyr	A1 a 330	Asp	Tyr	He	Ser	A1a 335	Asp
Glu	Leu	Ala	G1n 340	Val	Glu	Gln	Met	Leu 345	Ala	His	Leu	Thr	Ser 350	Ala	Ser
Ala	Gln	A1a 355	Ala	Ala	Ala	Ser	Leu 360	Pro	Thr	Ser	Glu	G1u 365	Asp	Ser	Ala
Pro	Ser 370	Ala	Met	Pro	Thr	Pro 375	Ser	Leu	Leu	Cys	Ser 380	Ser	Pro	Val	Ala
Thr 385	Ser	Pro	Ala	Lys	Pro 390	Val	Ser	Thr	Ser	Thr 395					
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145					150					155					160	
					aca Thr				-						-	528
-					cta Leu		-	-		_		_				576
	,	_	_	_	tgg Trp		_		-				-	-		624
				_	ata Ile			-								672
	-		_		att Ile 230	-	-		-					-		720
					gcc Ala					-	_		-			768
	_		_		aac Asn	_						-				816
		-	-		att Ile	_		-	_	_		-				864
-	-		-		tta Leu		_				•			•		912
			_		tac Tyr 310			-	_	-						960
-				-	gta Val			-				-	_	-		1008

350

325 330 335 agt ggt aaa tgc cct ctt cca agg caa caa gta aca gaa att ata ttt 1056 Ser Gly Lys Cys Pro Leu Pro Arg Gln Gln Val Thr Glu Ile Ile Phe 345 340 350 gtt tta aaa gca gtc agt act ctt att gat tca ctt aag aaa act cag 1104 Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys Thr Gln 360 365 355 cct gag aat gtt gat gga aat acc tgg gca caa gta att gcc tta tac 1152 Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala Leu Tyr 370 375 cca act tta gta gaa tgc atc acc tgt tct tct tca gaa gtc tgt tct 1200 Pro Thr Leu Val Glu Cys Ile Thr Cys Ser Ser Ser Glu Val Cys Ser 385 390 395 400 gca ctt aaa gag gca cta gtt cct ttt aag gat ttc atg cag cca cca 1248 Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe Met Gln Pro Pro 410 405 415 gca tcc aga gtt caa aat gga gaa tct tga 1278 Ala Ser Arg Val Gln Asn Gly Glu Ser * 425 420 <210> 238 <211> 425 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(425) <223> Xaa = Any Amino Acid <400> 238 Met Asp Asp Leu Gln Lys Leu Gly Val Ile Leu His Ser Ala Ile Ser Val Pro Ile Ser Ser Asp Ala Ser Pro Phe Ile Leu Pro Ser Tyr Thr 25 30 Glu Ala Val Leu Thr Ser Leu Gln Glu Ala Val Leu Thr Ala Leu Asp

40

45

Val	Leu 50	Gln	Lys	Ala	Ile	Cys 55	Val	Gly	Pro	Glu	Asn 60	Met	Gln	Ile	Met
Tyr 65	Pro	Ala	Ile	Phe	Asp 70	Gln	Leu	Leu	Ala	Phe 75	Val	Glu	Phe	Ser	Cys 80
Lys	Pro	Pro	Gln	Tyr 85	Gly	Gln	Xaa	Glu	Thr _. 90	Lys	His	Ile	Ala	Asn 95	Ala
Lys	Tyr	Asn	Gln 100	Пe	Gln	Leu	Phe	Ala 105	Pro	Ala	Glu	Trp	Val 110	Ala	Leu
Asn	Tyr	Val 115	Pro	Phe	Ala	Glu	Arg 120	Ser	Leu	Glu	Val	Val 125	Val	Asp	Leu
Tyr	Gln 130	Lys	Thr	Ala	Cys	His 135	Lys	Ala	Val		Asn 140	Glu	Lys	Val	Leu
G1n 145	Asn	Ile	Ile	Lys	Thr 150	Leu	Arg	Val	Pro	Leu 155	Ser	Leu	Lys	Tyr	Ser 160
Cys	Pro	Ser	Glu	Ser 165	Thr	Trp	Lys	Leu	Ala 170	Val	Ser	Ser	Leu	Leu 175	Arg
Val	Leu	Ser	Ile 180	Gly	Leu	Pro	Val	Ala 185	Arg	Gln	His	Ala	Ser 190	Ser	Gly
•		195					200					205	Glu	·	
	210		-			215		•			220		Gln		
225					230					235			Пe		240
				245					250				Val	255	
			260					265					Ser 270		
		275				,	280					285	Phe		
	290					295					300		Lys		
305				•	310			_		315			Val		320
				325					330				Glu	335	
	_	-	340					345					Ile 350		
Val	Leu	Lys 355	Ala	Val	Ser	Thr	Leu 360	Ile	Asp	Ser	Leu	Lys 365	Lys	Thr	Gln
	370			·		375					380		Ala		
Pro 385	Thr	Leu	Val	Glu	Cys 390	Пе	Thr	Cys	Ser	Ser 395	Ser	Glu	Val	Cys	Ser 400

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Ala	Leu	Lys	Glu	Ala 405	Leu	Val	Pro	Phe	Lys 410	Asp	Phe	Met	G1ņ	Pro 415	Pro	
Ala	Ser	Arg	Va1 420	Gln	Asn	Gly	Glu	Ser 425								
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_		_		-		_		_	-				gaa Glu 30		-	96
													ctg Leu			144
-		-				_							att Ile			192
		•				Arg			-	-			tgg Trp			240
	-		-	-				-					gtc Val			288
					-		-	_			_		gtc Val 110			336
tgg	ttg	gct	aaa	9 99	ctt	gga	gct	tgt	acc	tcc	agg	CCC	ata	cat	cct	384

WO 01/29221

Trp	Leu	Ala 115	Lys	Gly	Leu	Gly	Ala 120		Thr	Ser	Arg	Pro 125	Ile	His	Pro		
											cac His 140					•	432
											atg Met						480
											gct Ala					!	528
											cag Gln					!	57 6
											ctt Leu					,	624
											cat His 220						672
											gca Ala						720
											cgc Arg						768
											gtg Val						816
											gct Ala						864
aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	caa	gga		912

Thr	Gly 290	Glu	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	A1a 300	Ala	Ser	Gln	Gly	·
	aat Asn	_			-	_		-			-	-				960
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	atc Ile													taa *		1053
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	Phe	Ala	G1u 20		Trp	Asp	Asn	Va1 25		Leu	Leu	Val	G1u 30		Ser	
Pro	Pro	His 35		Val	Asn	Thr	Leu 40		Leu	Thr	Asn	Asp 45		Thr	Glu	
G1u	Va1 50		Glu	Glu	Val.	Leu 55		Lys	Lys	Ala	Asp 60		Пе	Leu	Ser	
Tyr 65	His	Pro	Pro	Пе	Phe 70		Pro	Met	Lys	Arg 75		Thr	Trp	Asn	Thr 80	
	Lys	Glu	Arg	Leu 85		Ile	Arg	Ala	Leu 90		Asn	Arg	Val	G1y 95		
Tyr	Ser	Pro	His 100		Ala	Tyr	Asp	Ala 105		Pro	Gln	Gly	Val 110		Asn	
Trp	Leu	Ala 115		Gly	Leu	Gly	Ala 120		Thr	Ser	Arg	Pro 125		His	Pro	
Son			_		т	Dro		Glu	Glv	Asn	His		Val	Glu	Phe	
261	Lys 130	Ala	Pro	Asn	tyr.		1111	uiu	4.5			_				
	Lys 130 Val					135					140					

Glu	Glu	Gin	1hr 180	Arg	He	Asn	Leu	Asn 185	Cys	Ihr	GIn	Lys	Ala 190	Leu	Met	
Gln	Val	Val 195	Asp	Phe	Leu	Ser	Arg 200	Asn	Lys	Gln	Leu	Tyr 205	Gln	Lys	Thr	
Glu	Ile 210	Leu	Ser	Leu	Glu	Lys 215	Pro	Leu	Leu	Leu	His 220	Thr	Gly	Met	Gly	
Arg 225		Cys	Thr	Leu	Asp 230		Ser	۷a۱	Ser	Leu 235	Ala	Thr	Met	Пe	Asp 240	
Arg	Ile	Lys	Arg	His 245	Leu	Lys	Leu	Ser	His 250	Пe	Arg	Leu	Ala	Leu 255	Gly	
Val	Gly	Arg	Thr 260	Leu	Glu	Ser	Gln	Va1 265	Lys	Val	Val	Ala	Leu 270	Cys	Ala	
Gly	Ser	G1y 275	Ser	Ser	Val	Leu	G1n 280	Gly	Val	Glu	Ala	Asp 285	Leu	Tyr	Leu	
Thr	G1 <i>y</i> 290	Glu	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	A1a 300	Ala	Ser	Gln	Gly.	
Ile 305	Asn	Val	Ile	Leu	Cys 310	Glu	His	Ser	Asn	Thr. 315	Glu	Arg	Gly	Phe	Leu 320	
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_	gac Asp	•			_	Ğlu	_	_			-		24	.0
	ctg Leu	-	-										28	8
-	aac Asn	His		-			-	-		_		-	33	6
	ctg Leu		_		_	-			 _				38	4
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	tca Ser												57	6
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					-	_								agc Ser 255		768
														ctg Leu		816
														gac Asp		864
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Gln	Val	Va1 35		Glu	Ser	Leu	Tyr 40		Ilе	Ser	Cys	Tyr 45		Thr	Leu	
Val	G1u 50		Met	Met	Glu	Pro 55		Pro	Leu	Ser	Thr 60		Pro	Lys	He	
Ser 65		Asp	Thr	Pro	Leu 70		Met	Met	Thr	Ser 75		Arg	Ala	Ser	Trp 80	
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358

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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
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Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
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                                           140
Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
145
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                                        155
His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
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Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Ser Val Leu Gln
                                185
Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
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                                                205
Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
                        215
                                            220
Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Arg Gly
                    230
                                        235
Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
                                   250
                245
Thr Leu Leu Glu Val Cys Gly Ser Trp Pro Glu Gly Phe Gly Leu Arg
                                265
His Met Ser Ser Met Glu His Thr Glu Glu Gly Ser Gly Ser Asp Leu
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Pro Thr Pro Trp Pro Ser His Leu Ala Gly Thr Ser Trp Asp Pro Glu
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Gln Thr Gln Pro Leu Thr
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										agc Ser						144
						-	_			cgg Arg			_			. 192
										cag Gln 75						240
	_		_	_	_	_	_		_	cgc Arg		_			_	288
	-	-		_	-	-	_	_		ccc Pro		Lys	_	-	-	336
										gcc Ala						384
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Arg Tyr Glu Pro Ser Asp Lys Asp Arg Gln Ser Pro Pro Pro Ala Lys
Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
                        55
Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
Ser Lys Ser Ser Ser Lys Val Thr Ser Val Pro Gly Lys Ala Ser Asp
                                105
Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
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Arg Glu Glu Leu Leu Lys Gln Leu Lys Ala Val Glu Asp Ala Ile Ala
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Arg Lys Arg Ala Lys Ile Pro Gly Lys Ala
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Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
                 5
1
                                                          15
ctc ctc gca ggg ctt gca cta ctg gga gtc ggg ccg gtc cca gcg cgg
                                                                       96
Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
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192		gat Asp	_	_	_	-				-			-			
240	-	gac Asp	-	_					-		_	-		_		
288		aat Asn 95	_			_	_	_							_	
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384	_	aag Lys	-								-		-	_	-	
432		gat Asp										-	-			
480		cta Leu			-									_		
528		aca Thr 175		_												
576		tgg Trp									_		_			_
624	-	cat His					-	-		-				-	_	

	195					200					205				
	-	_		_	gat Asp 215			-	_			_	•		672
•	-			-	acc Thr		-		-			•		_	720
-				-	agt Ser			_	-					-	768
					gca Ala			-		-		-			816
			_		ggc Gly	-					-		-	-	864
				-	tct Ser 295		-	_	-		-		-		912
				-	ggc Gly										960
					gaa Glu										1008
			-	_	ggc Gly			_	-		-			-	1056
					cag Gln								-		1104
					gaa Glu			_					-		1152

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	-	-		-						gat Asp 395	-	-	-	-		1200
		_			•	-				gac Asp					Ser	1248
										cat His						1296
	-	-	-	-			-		_	att Ile	_		-		_	1344
-			-	_		_	-			ccc Pro						1392
					_				-	gat Asp 475	-				-	1440
				_				_		tcc Ser	-			-		1488
										cgg Arg	_	-				1536
_				-				-		tct Ser						1584
_			-			_				aat Asn		_			_	1632
						-		_		tgg Trp					tat Tyr	1680

545					550					555					560	
	aca Thr					-										1728
	tgt Cys				_	-									_	1776
_	aaa Lys	-	_	_	-	-										1824
	gat Asp 610			tga *												1839
	<	210> 211> 212>	612													
		213>		s ap	oiens	5										
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1 Leu	/	213> 400> Ala Ala His	Homo 246 Ala Gly 20	Gly 5 Leu	Arg Ala	Leu Leu	Leu Glu	Gly 25	10 Val	Gly	Pro	Val Glu	Pro 30	15 Ala	Arg	
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1 Leu Ala Thr Phe 65	Ala Leu Leu Leu Leu	213> 400> Ala Ala His 35 Ala	Homo 246 Ala Gly 20 Asn Ala Arg	Gly 5 Leu Val Phe Glu Phe	Arg Ala Thr Gly Arg 70	Leu Leu Ala Asp 55 Asn	Leu Glu 40 Leu Asp	Gly 25 Leu Asn Leu	10 Val Phe Ser Ile Lys	Gly Gly Asp Val 75	Pro Ala Lys 60 Phe	Val Glu 45 Gln Leu	Pro 30 Ala Thr	15 Ala Trp Asp Asp	Arg Gly Leu Gln 80	
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Met	Val	Val	G1y 260	Gln	Ser	Ala	Phe	Ala 265	Asp	Phe	Asp	Gly	Asp 270	Gly	His
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				405					410				Val	415	
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Phe	Glu	Ala 435	Asp	Ala	Tyr	Phe	Va1 440	Lys	Val	Пe	Val	Leu 445	Ser	Gly	Leu
Cys	Ser 450	Asn	Asp	Cys	Pro	Arg 455	Lys	He	Thr	Pro	Phe 460	Gly	Val	Asn	Gln
Pro 465	Gly	Pro	Tyr	Пе	Met 470	Tyr	Thr	Thr	Val	Asp 475	Ala	Asn	Gly	Tyr	Leu 480
Lys	Asn	Gly	Ser	A1a 485	Gly	Gln	Leu	Ser	G1n 490	Ser	Ala	Hiś	Leu	A1a 495	Leu
Gln	يبط ا	Dro	Tyr	۸cn	Val	ىنم ا	GTV	Lou	Glv	۸na	Sar	د ۲۸	Acn	Dho	Lau

			500					505					510			
Asp	His	Leu 515	Tyr	Val	Gly	Ile	Pro 520	Arg	Pro	Ser	Gly	G1u 525	Lys	Ser	Ile	
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Leu	Thr	Pro	Ser	Asn 565	Ile	Val	Leu	Leu	Thr 570	Ala	Ile	Ala	Leu	Ile 575	Gly	
۷a٦	Cys	Val	Phe 580	Ilе	Leu	Ala	Ile	Ile 585	Gly	Пe	Leu	His	Trp 590	Gln	Glu	
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		_	-				_					act Thr				192
_			gat Asp				-					ttt Phe				240

65					70					75					80	
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		_			tca Ser	_										336
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	-	-			cag Gln	_	-								-	432
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Thr	Leu	Cys 35		Gly	Leu	Tyr	Phe 40		Glu	Phe	Val	Ser 45		Ser	Ala	
Phe	Leu 50		Ser	Leu	Leu	11e 55		IJе	Val	Tyŗ	Cys 60		Pro	Phe	Tyr	
G1u 65		Val	Asp	Thr	Thr 70		Val	Lys	Ser	Ser 75		Phe	Tyr	Ile	Thr 80	
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Thr	His	Asp	Arg 100		Ser	Ala		Ile 105		Ala	Пe	Val	Phe 110		Phe	
ם[ז	Ala	Ser		Met	Phe	Leu			Phe	He	Thr	Met		Tyr	Glu	

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	gat Asp		-												624
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Phe His Met	Pro Ile Thr		Gln Gly A		Gly Ile
	Gln Phe Asp				Val Cys

Ala 65	Pro	Glu	Ser	Leu	His 70	Thr	Val	His	Ala	Ala 75	Leu	Ile	Ser	Val	G1u 80
Lys	Ile	Pro	Tyr	Phe 85	Arg	Gly	Pro	Leu	G1n 90	Thr	Lys	Ala	Lys	Phe 95	His
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Pro	Ala	Pro 115	Asp	Asn	Phe	Asp	Gln 120	Glu	Pro	Ile	Leu	Asp 125	Ser	Phe	Asn
Phe	Ser 130	Gln	Glu	Tyr	Leu	Phe 135	Gln	Glu	Gln	Tyr	Leu 140	Ser	Lys	Asp	Leu
Thr 145	Pro	Ala	Val	Thr	Asp 150	Asn	Asp	Glu	Ala	Asp 155	Lys	Lys	Ala	Gly	Gln 160
Ala			-	165					170	•				175	
Glu			180					185					190		
Leu	•	195					200					205			
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225	•		•		230	_				235			Leu		240
				245					250				Phe	255	
Glu			260					265					270		
Gly		275	-			·	280					285			
	290					295					300		Lys		
Thr 305				-	310					315					320
Arg				325					330					335	
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372

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_	-	•				_		-				-	-	gat Asp 175		528
	-	_			gat Asp	_					_	tag *				567
÷		210> 211> 212> 213>	188 PRT	o sap	oiens	S .			•					•		
Met		400> Ala	-	Ala	Phe	Ala	Gly	Ala	Val	Arg	Ala	Ala	Ser	Gly	Ile	
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Lys	Asn	A1 a 35		Leu	Ile	Ser	Ala 40		Ser	Thr	Gly	Arg 45		Ser	His	
Ile	G1n 50	Thr	Pro	Val	Val	Ser 55	Ser	Thr	Pro	Arg	Leu 60	Thr	Thr	Ser	Glu	
Arg 65	Asn	Leu	Thr	Cys	Gly 70	His	Thr	Ser	Val	Ile 75	Leu	Asn	Arg	Met	Ala 80	
Pro	Val	Leu	Pro	Ser 85	Val	Leu	Lys	Leu	Pro 90	Val	Arg	Ser	Leu	Thr 95	Tyr	
Phe	Ser	Ala	Arg 100	Lys	Gly	Lys	Arg	Lys 105	Thr	Val	Lys	Ala	Val 110	Ile	Asp	
Arg	Phe	Leu 115	Arg	Leu	His	Cys	Gly 120	Leu	Trp	Val	Arg	Arg 125	Lys	Ala	Gly	
Tyr	Lys 130		Lys	Leu	Trp	Lys 135	Lys	Thr	Pro	Ala	Arg 140	Lys	Lys	Arg	Leu	
Arg 145	Glu	Phe	Val	Phe	Cys 150	Asn	Lys	Thr	Gln	Ser 155	Lys	Leu	Leu	Asp	Lys 160	
Met	Thr	Thr	Ser	Phe 165	Trp	Lys	Arg	Arg	Asn 170	Trp	Tyr	Val	Asp	Asp 175	Pro	
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gag gag gtg gta gcc gag aag cgt gcc ctg agc gcc aat ctc tac aag Glu Glu Val Val Ala Glu Lys Arg Ala Leu Ser Ala Asn Leu Tyr Lys 35 40 45	144
gcg gcc ggt ggt gcc gct acc aag aag ccc aag aag aag gaa ctt aag Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Glu Leu Lys 50 55 60	192
cgc gaa aag aag caa cgt cag cgg gaa cag cag agg gat gtg aac aac Arg Glu Lys Lys Gln Arg Gln Arg Glu Gln Gln Arg Asp Val Asn Asn 65 70 75 80	240
gag ccg gaa cca gag gaa gcc gaa gac tac tcc gat ggt cag tcg gag Glu Pro Glu Pro Glu Glu Ala Glu Asp Tyr Ser Asp Gly Gln Ser Glu 85 90 95	288
ggt cag ggc tcc gtg gct ggc gag gaa ccc ggt ctc tcc aag cag cat Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His 100 105 110	336
gtt gaa ttt gaa ccc gat gca gag gtc ctc act gat cag cga cga ccc Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro 115 120 125	384
agt agc gtg gct gag aag gag aac caa cct tct ggg gct ggc aaa aag Ser Ser Val Ala Glu Lys Glu Asn Gln Pro Ser Gly Ala Gly Lys Lys 130 135 140	432
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375

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Glu Glu Val Val Ala Glu Lys Arg Ala Leu Ser Ala Asn Leu Tyr Lys
Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Glu Leu Lys
                                            60
                        55
Arg Glu Lys Lys Gln Arg Gln Arg Glu Gln Gln Arg Asp Val Asn Asn
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                                        75
Glu Pro Glu Pro Glu Glu Ala Glu Asp Tyr Ser Asp Gly Gln Ser Glu
                                    90
Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
                                105
Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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145
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								atg Met		144
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96

						aat Asn 40							144
						gtc Val							192
	-		•		•	aaa Lys	-				 _		240
-	-	-	-			cac His							288
				•		ccc Pro	_	-	-	-			.336
	-	_		_	-	atc Ile 120		-	-				384
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<213> Homo sapiens

<400> 258

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Ala	Pro 50		Thr	Asn	Asn	Leu 55	Val	Ile	Ala	His	Ser 60	Asp	Gln	Gln	Val		
Phe 65	Glu	Tyr	Ser	Пe	Pro 70		Lys	Gln	Tyr	Thr 75		Trp	Ser	Arg _.	Thr 80		
	Gln	Lys	Gln	G1y 85		His	His	Leu	Trp 90	Leu	Gln	Arg	Asp	Thr 95			
Пe	Thr	His	Ile 100	Ser	Phe	His	Pro	Lys 105	Arg	Pro	Met	His	Ile 110	Leu	Leu		
His	Asp	Ala 115	Tyr	Met	Phe	Cys	Ile 120	Пe	Asp	Lys	Ser	Leu 125	Pro	Leu	Pro		
Asn	Asp 130	Lys	Thr	Leu	Leu	Tyr 135	Asn	Pro	Phe	Pro	Pro 140	Thr	Asn	Asp	Пе		
I1e 145	Ala	Gln	Leu	Pro	Pro 150	Pro	Ile	Lys	Lys	Lys 155	Lys	Phe	Gly	Thr			
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	ctt Leu																144
_	ggc Gly 50			_	_	-											192
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	_		-	-										gcc Ala		336
														aca Thr		384
					-	_	-		_			_		ttg Leu	-	432
-	_	-								_	_		_	gct Ala	gcc Ala 160	480
	_	-				-	-							atg Met 175		528
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taa *																627

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Glu	Leu	G1u 35	Ala	Ala	Leu	Gly	Lys 40	Lys	His	Lys	Gly	Gly 45	Asp	Ser	Ser	
Ser	G1y 50	Pro	G1n	Arg	Leu	Va1 55	Ser	Phe	Arg	Leu	Ile 60	Arg	Asp	Leu	His	
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		-	_	-		-		-	-			_		gac Asp		336
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			_	_	-	-				-		_	_	ttt Phe		432
									-				_	ggc Gly		480
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-		_	_			_			-					gcc Ala		576
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			-	-	_	-	-	att Ile					-	_	•	768
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-			_	-			-	atc Ile		_			-	_	_	864
		-						gcc Ala			-					912
								999 Gly	-		-			_		960
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295

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Glu	Ser	Trp	G1n 340	Gln	Ser	Cys	Glu	G1y 345	Tyr	G1u	Glu	Thr	Asp 350	Ile	Leu		
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				Gln						-		-		ctg Leu		ž	240
														ctg Leu 95		2	288
cga	999	gag	cta	cag	cga	gtc	сса	acc	ctg	cta	ctg	ссс	atg	cct	acg	(336

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				tca Ser												•	432
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				gct Ala 165													528
		_	_	gtg Val		_											576
				ctg Leu											cct Pro	••	624
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				ctc Leu													720
				cac His 245													768
_			•	gtc Val		-	_		_				_				816
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Gly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	
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					_	•			gcg Ala		_		_	,	_	960
	~ ~			-	-	-		-	cat His 330	-		-				1008
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Glu	Arg	Thr 35	Ser	Gly	Gly	Pro	Glu 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Ser	Leu 50	Gly	Ser	Ser	Arg	Va1 55	Pro	Arg	Cys	Gly	Gln 60	Gly	Thr	Leu	Leu
Ala 65	Gln	Ala	Cys	Gln	Asp 70	Leu	Pro	Ser	Ile	Arg 75	Asn	Cys	Tyr	Leu	Thr 80
His	Cys	Ser	Pro	A1a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
Arg	Ģly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr
		115					120					125		Arg	
Tyr	His 130	Arg	Ala	Ser	Asp	Thr 135	Pro	Ser	Gly	Leu	Ser 140	Pro	Thr	Asp	Thr
Met 145	Gly	Thr	Ala	Met	Arg 150	Val	Leu	Gln	Trp	Val 155	Leu	Val	Leu	Glu	Ser 160
•	-			165		·			170					Leu 175	
			180					185					190	Glu	
Pro	Val	G1n 195	His	Leu	Val	Ala	Ala 200	Leu	Leu	Ala	Gln	Leu 205	Cys	G1n	Pro
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Ser 225	Phe	Pro	Asp	Leu	Tyr 230	Ala	Asn	Phe	Leu	Asp 235	His	Phe	Glu	Ala	Val 240
		·	•	245			•		250					Leu 255	
	_		260					265				•	270	His	
Gly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser
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305	-		•		310					315				Trp	320
Pro	Val	Leu	Tyr	A1a 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	Ile 335	Phe
		•	340				·	345		-			350	Arg	
Met	Leu	G1n 355	Lys	Thr	Trp	Leu	Leu 360	Ala	Asp	Glu	Gly	Leu 365	Arg	Gln	His

Leu 385	370 Tyr	Ser	Gln	Leu	Leu Pro 390 Gln	375 Pro	Leu	Arg	Gln	His 395	380 Tyr				
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	-	_			gga Gly 70		_	-				_		-	240
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				-	agg Arg										336

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										gat Asp				-		_	432
		_				-	_			ggg Gly	_	_		_		-	480
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i	Gly	Phe		Gly					Glu	Lys					Gly	Gly	
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	Ser	Cys	Ile		Gln	Arg	Lys	Cys		Val	Thr	Ala	Thr		Leu	Lys	

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G1u 145		Glu	Val	Thr	Ala 150		Asn	Asp	Gly	Ala 155	Ala	Thr	Asp	Gly	Val 160	
Cys	Pro	Gln	Pro	Glu 165	Pro	Ser	Asp	Pro	Asp 170	Ala	G1n	Thr	Пe	Lys 175	Glu	
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	_	-									tat Tyr 60		_			192
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			_	-	-		-	_			agg Arg			-		288
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Gln	Val	Leu 35	Ser	Pro	Gly	Asp	Ile 40	Arg	Tyr	Пе	Phe	Thr 45	Ala	Thr	Pro	
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	Phe	Пe	Gln	Asp 85		Пе	Ala	Leu	Va1 90		Arg	Gly	Gly	Cys 95		
Phe	Leu	Ser	Lys 100		Arg	Val	Val	Gln 105		His	Gly	Gly	Arg 110		Val	

Пе	Пе	Ser 115	Asp	Asn	Ala	Val	Asp 120	Asn	Asp	Ser	Phe	Tyr 125	Val	Glu	Met	
	130	•				135			•		140			Phe		
145					150				•	155				His	160	•
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				-	gtg Val		-		-	 -		_		-	432
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		_		_	cac His		_			-	-	_	_		576
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		_			att Ile	-	-						-		768
		_		_	ggc Gly										816

WO 01/29221

	-					_		_						tat Tyr	_	864
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			-			_						-		tac Tyr		1104
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Ser	Lys 210	Ala	Ala	Leu	Ala	Leu 215	Gly	Leu	Leu	Gly	Val 220	Tyr	Cys	Tyr	Arg	

Ala Ala Ile Gly Ser Val Arg Phe Pro Trp Arg Pro Asp Ser Lys Asp 225 230 235 Ile Ser Lys Gly Ile Ile Glu Ala Arg Phe Val Tyr Val Phe Val Leu 245 250 Gly Ile Leu Phe Thr Gly Thr Lys Asp Leu Leu Lys Ser Gln Val Ile 265 Ala Ala Asp Phe Lys Leu Lys Thr Val Gly Leu Trp Glu Ile Tyr Ser 280 Gly Leu Val Leu Leu Ala Ala Leu Leu Phe Arg Pro His Asn Leu Pro 295 300 Val Leu Ala Phe Ser Leu Leu Ile Gln Thr Leu Met Thr Lys Phe Ile 310 315 Trp Lys Pro Leu Arg His Asp Ala Ala Glu Ile Thr Val Met His Tyr 325 330 Trp Phe Gly Gln Ala Phe Phe Tyr Phe Gln Gly Asn Ser Asn Asn Ile 345 Ala Thr Val Asp Ile Ser Ala Gly Phe Val Gly Leu Asp Thr Tyr Val 360 Glu Ile Pro Ala Val Leu Leu Thr Ala Phe Gly Thr Tyr Ala Gly Pro 375 380 Val Leu Trp Ala Ser His Leu Val His Phe Leu Ser Ser Glu Thr Arg 390 395 Ser Gly Ser Ala Leu Ser His Ala Cys Phe Cys Tyr Ala Leu Ile Cys 405 410 Ser Ile Pro Val Phe Thr Tyr Ile Val Leu Val Thr Ser Leu Arg Tyr 420 425 His Leu Phe Ile Trp Ser Val Phe Ser Pro Lys Leu Leu Tyr Glu Gly 440 445 Met His Leu Leu Ile Thr Ala Ala Val Cys Val Phe Phe Thr Ala Met 455 460 Asp Gln Thr Arg Leu Thr Gln Ser 470 <210> 271 <211> 1089 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1089) <221> misc_feature <222> (1)...(1089)

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_	_	_	-	_										atc Ile		336
			-	-			_	-						acc Thr		384
_			_			-				_	_	-	-	tcc Ser		432
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			_								aac Asn				_	624
				-		_	_				gct Ala 220	_	_	_		672
_			_								ctc Leu					720
				-							atc Ile					768
	-	-		_				-		-	gta Val		-		_	816
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_	-		_	_	_		-	_		_	acc Thr 300	_	-		_	912
_				_	_	-	_		-	_	ccc Pro	_		_		960
	_	-		-			-	_	•		gac Asp		-	_		1008
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400

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Arg	Ala	Pro	Пe	Arg 245	Arg	Ala	Ala	His	Va1 250	Val	Пе	His	Gln	Ser 255	Leu	
Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	A1a 265	Ser	Leu	Val	Glu	Val 270	Asn	Pro	
Ala	Tyr	Ser 275	Val	Pro	Ser	Ser	G1n 280	Glu	Leu	Glu	Ala	Cys 285	Ile	Gly	Cys	
Met	Ġ1n 290	Thr	Arg	Ala	Ser	Va1 295	Lys	Leu	Val	Lys	Thr 300	Cys	Gln	Glu	Ala	
A1a 305	Thr	Gly	Glu	Cys	Gln 310	Gln	Cys	Tyr	Cys	Arg 315	Pro	Met	Trp	Cys	Leu 320	
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_		_	_	_	_	_				_		ctc Leu 95		288
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												cct Pro	-	432
												ctg Leu		480
												cac His 175		528
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Gln Pro Le	u Phe Arg	Gly Ala	Asp Al	rg Tyr	Asp Ph	ne Ala 45	Ile	Met	Ile	
Pro Pro G1 50	y Gly Thr	Glu Cys 55	Phe T	rp Gln	Phe Al		Gln	Thr	Gly	
Tyr Phe Ty 65	r Phe Ser	Tyr Glu 70	Val G	iln Arg	Thr Va	al Gly	Met	Ser	His 80	
Asp Arg Hi	s Val Ala 85	a Ala Thr	Ala H	lis Asn 90	Pro G1	ln Gly		Leu 95	Ile	
Asp Thr Se	r Gln Gly 100	√Val Arg	-	in Ile .05	Asn Ph	ne Ser	Thr 110	Gln	Glu	
Thr Gly Ph		ı Leu Cys	Leu So 120	er Asn	Gln Hi	is Asn 125	His	Phe	Gly	
Ser Val Gl 130	n Val Tyr	Leu Asn 135		ily Val	Phe Ty		Gly	Pro	Glu	
Thr Asp Hi 145	s Lys Glr	n Lys Glu 150	Arg L	ys Gln	Leu As 155	sn Asp	Thr	Leu	Asp 160	
Ala Ile Gl	u Asp Gly 165		Lys V	'al Gln 170	Asn As	sn Ile		His 175	Met	
Trp Arg Ty	r Tyr Asr 180	Phe Ala	_	let Arg .85	Lys Me	et Ala	Asp 190	Phe	Phe	
Leu Ile Gl		ı Tyr Asn	Tyr V. 200	al Asn	Trp Tr	rp Ser 205	Thr	Ala	Gln	
Ser Leu Va 210	l lle lle	e Leu Ser 215	_	le Leu	Gln Le		Phe	Leu	Lys	
Arg Leu Ph	e Asn Val			hr Asp			Pro	Arg	Cys	

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					agg Arg 70									240
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					ctg Leu									336

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		-	_	-	tca Ser										432
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					aac Asn										528
	-	-	_	-	gtg Val										576
_	-		_	-	acc Thr		-	_	-	_		_	,	_	624
-	-				ctg Leu	-	_				-	-		_	672
		_	_		ggc Gly 230	-	-	_			 				720
		_	_		ctg Leu										768
					ctg Leu										816
-	Ala	-	-		ctg Leu								_		864

					cag Gln											912
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Ala	Met	Ile	Gly 100	Gly	Leu	Asp	Asp	Gly 105	Asp	Asn	Pro	His	Ser 110	Pro	Val	
Ala	Leu	G1u 115	Ala	Met	Leu	Gly	Leu 120	Ala	Arg	Leu	Val	His 125	Leu	Val	Glu	
Ser	Trp	Asp	Leu	Arg	Ser		Leu	Leu	His	۷al		Ιle	Arg	Ile	Arg	
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Leu	Phe	Gly	His	Leu 165	Asn	Lys	Va1	Cys	His 170	Gly	Asp	Cys	Glu	Asp 175	Val	
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Lys 225	His	Leu	Gln	Glu	G1 <i>y</i> 230	Arg	Ala	Leu	His	Phe 235	Gly	Glu	Phe	Leu	Asn 240	
Thr	Thr	Cys	Lys	His 245	Leu	Met	His	His	Phe 250	Pro	Asp	Leu	Leu	Gly 255	Arg	
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	Trp	G1u 270	Asn	۷al	
Arg	Ala	A1a 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu	
Pro	Arg 290	Gln	Gln	Pro	Gln	Va1 295	Asp	Leu	Asp	Gln	Leu 300	IJе	Ala	Ala	Leu	
305				_	Asp 310					Val 315	Arg	Thr	Arg	Ala	Ala 320	
Glu	Ala	Leu	Gly	Arg 325	Leu	Val	Lys	Leu	A1a 330							
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		212>														
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		220>														
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1	wsh	um	GIII	5	Arg	ч	Lys	PIU	10	Leu	Leu	Vai	rne	15	Sei	
		-	_	_	aca Thr	-		_		-	-		-		_	96
, 7 (1	141	, tru	20	mu	1111	, ii u	uiy	25	LCU	0,3	LCU	1.0	30	110	ccu	
					cag Gln											144
Leu	ıyı	75 75	Leu	vai	uIII	ı yı	Leu	vai	MOII	riu	uly	Val	Leu	Arg	HIII.	

-	ccc Pro 50		-	_	_		_		-		_	-					192
	ttc Phe														-		240
	gtg Val		_	_	-				-			-		-	•	,	288
	atc Ile					_		-			-				-		336
	ctc Leu				-		-		-					_			384
	aaa Lys 130	-					-	_			-		_				432
-	ggc Gly	-	_				-	-		-		-	_	_			480
-	ctg Leu			_			_			-			•		_		528
	999 Gly		_	_	_								_				576
	ctt Leu								-					-	-		624
	gaa Glu 210				tga *												642

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Tyr	Pro	Pro	Gln	G1u 165	Ala	Asn	Arg	Ser	Ile 170	Thr	Ser	Leu	Ser	Val 175	Ala	
	act Thr															576
	cct Pro															624
	gat Asp 210															672
	gat Asp	_		-	_											720
	ctc Leu		-	_												768
	act Thr															816
_	aaa Lys	_			_		_	-								864
	ttg Leu 290															912
	cag Gln															960
	agt Ser															1008
gct	gca	cat	gaa	gct	gag	gaa	gaa	tct	gat	aat	att	gca	gaa	gac	ttc	1056

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Ala	Ala	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe	
					gaa Glu									_	_	1104
					cac His	-					-				-	1152
_			-	-	cac His 390	_				-			tag *			1194
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Gly	Ser	Pṛo	Gly 20	Gly	Leu	Thr	Ser	Leu 25	G1n	Gln	Gln	Lys	G1n 30	Arg	Leu	
Пe	Glu	Ser 35	Leu	Arg	Asn	Ser	His 40	Ser	Ser	Ile	Ala	Glu 45	Пe	Gln	Lys	
Asp	Val 50	Glu	Tyr	Arg	Leu	Pro 55	Phe	Thr	Ile	Asn	Asn 60	Leu	Thr	Ile	Asn	
Ile 65	Asn	He	Leu	Leu	Pro 70	Pro	Gln	Phe	Pro	G1n 75	Glu	Lys	Pro	Val	Ile 80	
Ser	۷a٦	Tyr	Pro	Pro 85	Ile	Arg	His	His	Leu 90	Met	Asp	Lys	Gln	G1y 95	Val	
Tyr	Val	Thr	Ser 100	Pro	Leu	Val	Asn	Asn 105	Phe	Thr	Met	His	Ser 110	Asp	Leu	
Gly	Lys	Ile 115	Ile	Gln	Ser	Leu	Leu 120	Asp	Glu	Phe	Trp	Lys 125	Asn	Pro	Pro	
Val	Leu 130	Ala	Pro	Thr	Ser	Thr 135	Ala	Phe	Pro	Tyr	Leu 140	Tyr	Ser	Asn	Pro	
Ser 145	Gly	Met	Ser	Pro	Tyr 150	Ala	Ser	Gln	Gly	Phe 155	Pro	Phe	Leu	Pro	Pro 160	•
	Pro	Pro	Gln	G1u 165	Ala	Asn	Arg	Ser	Ile 170		Ser	Leu	Ser	Val 175		

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Asp	Thr	Val	Ser 180	Ser	Ser	Thr	Thr	Ser 185	His	Thr	Thr	Ala	Lys 190	Pro	Ala		
Ala	Pro	Ser 195	Phe	Gly	۷a٦	Leu	Ser 200	Asn	Leu	Pro	Leu	Pro 205	Ile	Pro	Thr		
Val	Asp 210	Ala	Ser	Пе	Pro	Thr 215	Ser	Gln	Asn	Gly	Phe 220	Gly	Tyr	Lys	Met		
Pro 225	Asp	Val	Pro	Asp	Ala 230	Phe	Pro	Glu	Leu	Ser 235	Glu	Leu	Ser	Val	Ser 240		
Gln	Leu	Thr	Asp	Met 245	Asn	G1u	Gln	Glu	G1u 250	Val	Leu	Leu	Glu	G1n 255	Phe		
Leu	Thr	Leu	Pro 260		Leu	Lys	Gln	Ile 265		Thr	Asp	Lys	Asp 270		Leu		
Val	Lys	Ser 275	Ile	Glu	Glu	Leu	Ala 280	Arg	Lys	Asn	Leu	Leu 285	Leu	Glu	Pro		
Ser	Leu 290	Glu	Ala	Lys	Arg	G1n 295	Thr	Val	Leu	Asp	Lys 300	Tyr	Glu	Leu	Leu		
Thr 305	Gln	Met	Lys	Ser	Thr 310	Phe	Glu	Lys	Lys	Met 315	Gln	Arg	Gln	His	G1u 320		
Leu	Ser	Glu	Ser	Cys 325	Ser	Ala	Ser	Ala	Leu 330	Gln	Ala	Arg	Leu	Lys 335	Val		
Ala	Ala	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe		,
Leu	Glu	Gly 355	Lys	Met	Glu	Ile	Asp 360	Asp	Phe	Leu	Ser	Ser 365	Phe	Met	Glu		
Lys	Arg 370	Thr	Ile	Cys	His	Cys 375	Arg	Arg	Ala	Lys	G1u 380	Glu	Lys	Leu	Gln	ŕ	
G1n 385	Ala	Ile	Ala	Met	His 390	Ser	Gln	Phe	His	A1a 395	Pro	Leu					
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	<2	220> 221> 222>	CDS (1).	(5	579)							,					
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_					Pro			-									40
gtc	cgg	aac	agc	aag	aag	agg	ccg	gcc	agc	cct	tcc	cac	aat	ggc	agc		96

Val	Arg	Asn	Ser 20	Lys	Lys	Arg	Pro	Ala 25	Ser	Pro	Ser	His	Asn 30	Gly	Ser		
_												-		gct Ala		1	144
•			•			-	-	-	_	_	-			aaa Lys	_	1	192
														aaa Lys		2	240
														ggc Gly 95		2	288
-	-		_	_		-								atc Ile		3	336
-		-			-									tac Tyr		3	884
-		-	-					_		-		_		tct Ser	-	4	132
-			_		•				-		-	-		ctg Leu		4	180
	-			_	-									tct Ser 175		5	528
														gtt Val		5	576
tga																5	579

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-	ctg Leu				-									96
	ggt Gly													144
	act Thr 50													192
	caa Gln													240
	ccc Pro	_					_	-	-		-		-	288
	ttg Leu	Ser			-	_	_	-		_				336
	tgg Trp				-									384
	ctt Leu 130													432
	aag Lys													480
	aat Asn													528

			•			-					-		att Ile 190	-		576
_			-		-	_		-		_		-	aga Arg		_	624
			-			-	_	-		_	-	_	aaa Lys		•	672
					-	_		•	-	-	_	•	aga Arg		_	720
		-		_		_	-		-	-		•	aag Lys	•	~	768
		_		-	-	•			•		_		gag Glu 270			816
	_						_	_		-		-	aga Arg			864
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<211> 315

<212> PRT

<213> Homo sapiens

<400> 284

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Ala	Leu	Leu	G1n 20	Val	Asp	Ser	Gly	Ser 25	Gly	Ser	Asp	Ser	Glu 30	Pro	Gly
Lys	Gly	Lys 35	Gly	Arg	Asn	Thr	G1y 40	Lys	Ser	Gln	Thr	Leu 45	Gly	Ser	Lys
Ser	Thr 50	Thr	Aśn	Glu	Lys	Lys 55	Arg	Glu	Lys	Arg	Arg 60	Lys	Lys	Lys	Glu
G1n 65	Ğln	Gln	Ser	Glu	A1a 70	Asn	Glu	Leu	Arg	Asn 75	Leu	Ala	Phe	Lys	Lys 80
Пe	Pro	Gln	Lys	Ser 85	Ser	His	Ala	Val	Cys 90	Asn	Ala	Gln	His	Asp 95	Leu
Pro	Leu	Ser	Asn 100	Pro	Val	Gln	Lys	Asp 105	Ser	Arg	Glu	Glu	Asn 110	Trp	Gln
Glu	Trp	Arg 115	Gln	Arg	Asp	Glu	Gln 120	Leu	Thr	Ser	Glu	Met 125	Phe	Glu	Ąla
Asp	Leu 130	Glu	Lys	Ala	Leu	Leu 135	Leu	Ser	Lys	Leu	Glu 140	Tyr	Glu	Glu	His
145	Lys		•	•	150					155				•	160
	Asn			165					170					175	
	Thr		180			•		185			·		190		•
Lys	Thr	G1u 195	Glu	Val	Val	Leu	Lys 200	Asp	Gly	Arg	Ile	G1u 205	Arg	Leu	Lys
Leu	G1u 210	Leu	Glu	Arg	Lys	Asp 215	Ala	Glu	Пe	Gln	Lys 220	Leu	Lys	Asn	Val
225	Thr		·		230					235					240
	Leu		•	245					250		-	•	-	255	
He	Leu	Leu	G1n 260	Val	Asp	Glu	Ser	G1n 265	Ser	Ile	Lys	Asn	G1u 270	Leu	Thr
Ile	Gln	Val 275	Thr	Ser	Leu	His	A1a 280	Ala	Leu	Glu	Gln	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	Glņ	Ala	G1u 295	Leu	Ala	Lys	Tyr	G1n 300	Gly	Gly	Arg	Lys
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			aaa tgt ttg caa Lys Cys Leu Gln 60	-
			gat gag ggg gac Asp Glu Gly Asp	
		-	cac ata ggc gta His Ile Gly Val 95	_
			gga gtc ata ctg Gly Val Ile Leu 110	
	_	er Leu Thr Ser	tcc tcg gag aac Ser Ser Glu Asn 125	
cgg ata acc ggc q Arg Ile Thr Gly / 130	-			
ctt tgg aag cat g	ggg aat ctg cg	a aat gtg ctg	atc ttg atg gat	caa 480

Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	Gln 160	
	_		-			gcc Ala		-		_	-	_		_		528
						999 Gly				-		-			_	576
_		_		_		atc Ile		_		_				-	•	624
	-	-	_	_	-	agc Ser 215	_	_	_					_		672
-	-		_	•	-	gtg Val	-				_	_			_	720
		-				gaa Glu	-		_	-	_		_	_		768
						gac Asp	_	-					-			816
				_	-	gaa Glu			-	-	_					864
_				-		aac Asn 295		-			_	•	_	_	•	912
						ccc Pro										960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe	
	agg Arg			-											-	1056
	atc Ile											_				1104
	atc Ile 370															1152
	acc Thr															1200
-	ctc Leu		-		-		-	_	_		-	_	_	-	_	1248
-	gag Glu	-	-	-				_	-		-				-	1296
	cct Pro	_	taa *													1308
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	Lys		20		-			25					30			
Trp	Ser	His 35	Arg	Arg	His	Val	Met 40	G1n	Gln	Gly	Glu	G1n 45	G1n	Gln	Île	

Pro	Asp 50	Pro	Cys	Arg	Leu	Ser 55	Thr	Ala	Thr	Leu	Lys 60	Cys	Leu	Gln	Ala
G1n 65	Ala	Met	Arg	Glu	Gly 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asn 80
Leu	Trp	Thr	Leu	Leu 85	Ser	Ser	Pro	Ser	Thr 90	His	His	Ile	Gly	Val 95	Cys
Ser	Leu	Ala	Arg 100	Ser	Met	Ala	Val	Trp 105	Gln	His	Gly	Val	Ile 110	Leu	Asp
Ile -	Met	Glu 115	G1n	Leu	Leu	Ser	Ser 120		Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr
Arg	Ile 130	Thr	Gly	Ala	Ala	Phe 135	Phe	Ser	Glu	Leu	Met 140	Lys	Glu	Pro	Пе
Leu 14 5	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	Gln 160
Ser	Ala	Trp	Asp	Ser 165	Asn	Ala	Thr	Leu	Arg 170	Gln	Met	Ala	Пe	Arg 175	Gly
	-		180		Ser	_	•	185					190		•
		195			Ser		200	_	-			205			
	210			•	Glu	215		-			220				
Leu 225	Leu	Thr	Asp	Arg	Asp 230	Val	Ser	Phe	Tyr	Phe 235	Lys	Glu	Ile	Val	Leu 240
Gln	Thr	Arg	Thr	Phe 245	Phe	Glu	-	Glu	G1n 250	Asp	Asp	Val	Arg	Leu 255	Thr
			260		Glu			265				,	270		•
		275			Glu		280			•		285			
	290		•	•	Pro	295		-			300		-	-	•
305					Ile 310					315					320
		•		325	Leu			•	330					335	
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	A1a 345	Lys	Lys	Asn	Gln	G1u 350	Ile	Leu
Trp	He	Leu 355	His	Thr	His	Ser	Phe 360	Thr	Phe	Phe	Thr	Ser 365	Thr	Trp	Glu
Val	Ile 370	Arg	Ser	Ala	Ala	Va1 375	Lys	Leu	Thr	Asp	A1a 380	Val	Val	Leu	Asn
Leu 385	Thr	Ser	Gln	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395	Glu	Gln	Leu	Thr	Thr 400

Arg	Leu	Gln	Ala	Leu 405	Arg	Gln	Asp	Pro	Cys 410	Ile	Ser	Val	Gln	Arg 415	Ala	
Ala	Glu	Ala	A1a 420	Leu	Gln	Thr	Leu	Leu 425	Arg	Arg	Cys	Lys	G1u 430		Ser	
Пe	Pro	Leu 435														
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	_	_	-		gca Ala		_	_				_				96
					gca Ala		-	-			-	-			_	144
					ctg Leu	-		_		-		-				192
					gtg Val 70											240
	_	_	_		ttc Phe			-	-	_		-	-		_	288
					aag Lys		-	-	-						-	336

	gcc Ala															384
_	aca Thr 130						-			_	-				-	432
	tgg Trp	_	_	-	-	_							_		-	480
	ctc Leu	-		-	_	_				-	_	-	-	_	-	528
	agt Ser	-				_			Thr				-			576
	gca Ala			_				_					_		•	624
	tat Tyr 210				_	-	-		-							672
	ttt Phe															720
_	ctg Leu			_		_		-				-				768
	ttc Phe											Pro				816
tca Ser	tag *							•								822

425

<210> 288

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							gct Ala											96
	-					-	gac Asp		-		_	-	-	_	_			144
		-	_	_		-	gtg Val 55	-	-	-			_	-	_	gca. Ala		192
	_	_	_		_		ttg Leu								-	_	;	240
						Пe	aat Asn	His	Val	Lys	Glu	Glu	Arg	Pro		Lys	;	288
			-				ttg Leu	•		-			•	-		-	,	336
	-	_			-	-	gac Asp					-			_	-	;	384
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PCT/US00/29052

Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	G1n	Cys 140	Gly	Leu	Gln	Ala	
						aca Thr										480
						ttc Phe										528
	_		-			aaa Lys								:		576
-		-	_	-		gag Glu								-	-	624
	_					tgt Cys 215	_		_	-		_	_		_	672
		-	_	-	-	ctt Leu									_	720
	aga Arg		-			gag Glu	tag *									744
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Met		100> G1y		Ser	Ser	Ser	Asn	Ser	G1y	Ser	Thr	Gly	Phe	Ile	Ser	
1			_	5		Ala			10					15		
Cys	Ile	Asn 35	20 Ser	Gly	Met	Asp	Thr 40	25 Ala	Ser	Ser	Val	Ala 45	30 Leu	Asp	Leu	

Val	Glu 50	Ser	Gln	Thr	Glu	Va1 55	Ser	Ser	Glu	Tyr	Ser 60	Met	Asp	Lys	Ala	
Met 65	Val.	Glu	Phe	Ala	Thr 70	Leu	Asp	Arg	Gln	Leu 75	Asn	His	Tyr	Val	Lys 80	
Ala	Val	Gln	Ser	Thr 85	He	Asn	His	Val	Lys 90	Glu	Glu	Arg	Pro	G1u 95	Lys	
IJe	Pro	Asp	Leu 100	Lys	Leu	Leu	Val	Glu 105	Lys	Lys	Phe	Leu	Ala 110	Leu	Gln	
Ser	Lys	Asn 115	Ser	Asp	Ala	Asp	Phe 120	Gln	Asn	Asn	Glu	Lys 125	Phe	Val	Gln	
Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	Gln	Cys 140	Gly	Leu	Gln	Ala	
145	_			·	Gly 150					155		·			160	
				165	Asn			. 1.	170					175		
			180		Asn			185					190		·	
		195	_		Ile		200					205				•
	210				Gly	215				·	220				•	
225					A1a 230		Arg	Arg	Ala	11e 235	Glu	Asn	His	Asn	Lys 240	
Lys	Arg	His	Arg	His 245	Ser	Glu					•					
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		.66	(1).		,5,,											
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1	Ala	giu	1115	5	uly	רוט	AI Y	Leu	10	LCU	val	LEU	Lys	15	LCU	

				_		-			_				acc Thr		. 96
-		_	_	-	_	_				_		-	ctc Leu	-	144
	_	-	_	_	_		_		 -	-	_	_	gac Asp		192
										_	_		ctg Leu	-	240
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												-	cca Pro		336
	-		-	_	-				_			-	gtg Val		384
		_	_	_			_	-		_		-	atc Ile		432
													atc Ile		480
						_	-	-		-	-		gac Asp 175	Ψ.	528
													cac His		576

-	_		_	-		-	_	-	-	-			•	ctg Leu	_	624
_	-				•	•	_					-	-	ttc Phe	•	672
		-	_											ctc Leu		720
		_	_		_	-					_	-	_	ggc Gly 255	•	768
	_			Cys	_				_	_	_			aac Asn	-	816
-	-	-	-		_					-		_		tcg Ser		864
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<213> Homo sapiens

<220>

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His Pro Ser Thr Gly Pro Leu Arg Trp Ala Leu Leu Thr Leu

315

310

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		-	-					gcc Ala 25		-							96	
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								gta Val								1	.92	
		-	-	_	-	-		tac Tyr	-				-	_	-	2	40	
		-			_		-	tgg Trp		-	_					2	288	
								aga Arg 105								3	36	
								gag Glu								3	84	
				_	-	_		agt Ser						_		4	32	

				gct Ala									480
				atg Met									528
				cac His									576
				ctg Leu					_	_	_	_	624
				ttc Phe 215						-	-		672
_	_	 _	-	atg Met	 		_	•			_		720
				gcc Ala									768
				att Ile									816
				ctt Leu									864
				aga Arg 295									912
				gac Asp		Lys							960

434

ggc Gly	-			_					_	-				1008
ccg Pro		-	-		-		_	_	_	-		_		1056
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<211> 368

<212> PRT

<213> Homo sapiens

<400> 294

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				165					170					175		
Val	Tyr	Asp	Gln 180	Pro	Phe	His	Ser	Ser 185	Ala	Leu	G1u	Lys	Glu 190	G 1u	Ala	
Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu	
Ser	Glu 210	Lys	Ala	Lys	Glu	Phe 215	Leu	Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe	
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235	Leu	Ser	Leu	Ala	Asn 240	
Gln	Pro	Val	Ile	His 245	Ser	Ala	Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255	Lys	
Asp	Thr	Thr	Ser 260	Lys	Ala	IJе	His	Ser 265	Пe	Phe	Lys	Asn	Ala 270	Пe	Gln	
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Val 280	Phe	Gln	Lys	Asp	Asp 285	Gly	Phe	Asp	
	290	-			Thr	295		·		·	300			-		
305	-				G1n 310	•				315					320	
				325	His				330					335	-	
	-		340		Ala			345					350			
Asp	GIn	Ser 355	Asp	He	Val	Ser	1hr 360	Met	Glu	His	lyr	1yr 365	lhr	Ala	Phe	
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-		•	_	•	gtc Val	-				-		-		•		96

436

					ctt Leu	_	_	•	_	1	144
					aga Arg					1	İ92
Ser		-		-	aac Asn 75				-	2	240
					gaa Glu					2	288
					ggt Gly					3	336
					aac Asn					3	384
					gac Asp						132
					aag Lys 155				~ ~	. 4	180
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<211> 185

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437

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<213> Homo sapiens
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Val Ser Asn Asp Pro Asp Val Ile Lys Leu Gln Glu Ile Pro Thr Phe

48

20 25 30 cag ccc ctt ttg aaa ggg cta ttg agt ggc cag act tcc cca aca aat 144 Gln Pro Leu Leu Lys Gly Leu Leu Ser Gly Gln Thr Ser Pro Thr Asn 35 40 gcc aaa ttg gag aaa ctg gac tct cag cag gtg ttg cag ctc tgc ctc 192 Ala Lys Leu Glu Lys Leu Asp Ser Gln Gln Val Leu Gln Leu Cys Leu 50 55 60 cga tat caa gat cac ctg cat cag tgt gca gag gcc gtt gct ttt gac 240 Arg Tyr Gln Asp His Leu His Gln Cys Ala Glu Ala Val Ala Phe Asp 65 70 75 cag aat get ttg gtt aaa ega ate aaa gag atg gat etg tet gta gaa 288 Gln Asn Ala Leu Val Lys Arg Ile Lys Glu Met Asp Leu Ser Val Glu 85 act ctg ttc agc ttc atg cag gag cgc cag aaa aga tac gcc aag tat 336 Thr Leu Phe Ser Phe Met Gln Glu Arg Gln Lys Arg Tyr Ala Lys Tyr 100 105 ged gag dag atd dag aaa gtg aad gag atg ted ged atd etd egd egd 384 Ala Glu Gln Ile Gln Lys Val Asn Glu Met Ser Ala Ile Leu Arg Arg 115 120 125 ata cag atg ggc atc gac cag act gtg ccc ctg ctg gac agg ctc aac 432 Ile Gln Met Gly Ile Asp Gln Thr Val Pro Leu Leu Asp Arg Leu Asn 130 135 ago atg ctg ccc gag ggc gag cgg ctg gag ccc ttc ago atg aag ccc 480 Ser Met Leu Pro Glu Gly Glu Arg Leu Glu Pro Phe Ser Met Lys Pro 145 150 155 160 gac cgc gag ctc agg ctg tag 501 Asp Arg Glu Leu Arg Leu * 165

<210> 298

<211> 166

<212> PRT

<213> Homo sapiens

439

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			- 20					25					30				
•	-					tta Leu		-	-						_		144
-			-	_		gct Ala 55						-	-	-	_		192
	-	-	-	_		gga Gly	-				-	_	_				240
	-		_			aca Thr				_				_	-		288
	_			_		ctt Leu	_				_	-	•		-		336
-				-		tca Ser	-	-			_				-		384
					-	gcc Ala 135				-	_			_			432
	-	-	_			aga Arg			-	-		-	-				480
			-		-	ttt Phe				_	-	_			-		528
						gat Asp											576
						atg Met										Í	624

		195					200					205				
			gag Glu													672
			aca Thr				-		_			-		_		720
			cag G1n	-			-								•	768
			agc Ser 260						Ala					-		816
	tat Tyr		tga *													828
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Leu	Ala	Ala	Asp 20	Pro	Leu	Asn	Arg	Arg 25	Ala	Пe	Val	Gln	Asp 30	Gln	Gly	
		35	Gly				40		. '			45				
	50		Ala			55					60		•	_		
Asn 65	Arg	Glu	Lys	Met	Lys 70	Gly	Glu	Leu		Met 75	Met	Leu	Ser	Leu	G1n 80	

Asn	Val	He	Gln	Lys 85	Thr	Thr	Thr	Pro	G1y 90	Glu	Thr	Lys	Leu	Leu 95	Ala	
Ser	Glu	Пe	Tyr 100	Asp	Ile	Leu	Gln	Ser 105	Ser	Asn	Met	Ala	Asp 110	Gly	Asp	
Ser	Phe	Asn 115		Met	Asn	Ser	Arg 120	Arg	Arg	Lys	Ala	Xaa 125		Phe	Leu	
Gly	Thr 130		Asn	Lys	Arg	Ala 135		Thr	Val	Val	Leu 140		IJе	Asp	Gly	
Leu 145		Asp	Thr	Ser	Arg 150		Asn	Leu	Cys	Glu 155		Ala	Leu	Leu	Lys 160	
Пe	Lys	Gly	۷al	Ile 165	Ser	Phe	Thr	Phe	Gln 170	Met	Ala	Val	Gln	Arg 175	Cys	
Val	·Val	Arg	Ile 180	Arg	Ser	Asp	Leu	Lys 185	Ala	Glu	Ala	Leu	Ala 190	Ser	Ala	
Пe	Ala	Ser 195	Thr	Lys	Val	Met	Lys 200	Ala	Gln	Gln	Val	Va1 205	Lys	Ser	Glu	
Ser	Gly 210	Glu	Glu	Met	Leu	Val 215	Pro	Phe	Gln	Asp	Thr 220	Pro	Val	Glu	Val	
G1u 225	Gln	Asn	Thr	Glu	Leu 230	Pro	Asp	Tyr	Leu	Pro 235	Glu	Asp	Glu	Ser	Pro 240	
Thr	Lys	Glu	Gln	Asp 245	Lys	Ala	Val	Ser	Arg 250	Val	Gly	Ser	His	Pro 255	Glu	
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Phe	Tyr	Trp 275														
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_													gaa G1u 30			
				_				-					gga Gly	_	•	144
							_			-	_		aag Lys	_	-	192
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		_					-	-					cat His	-		288
	_				-	-	_						aat Asn 110			336
		_		_	_								ttt Phe		-	384
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	_			-	-	-	_					_	tcc Ser		_	480
-				-									gac Asp			528
		-				-			-	-	_		att Ile 190	-		576

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	-	_	~	-			-					-		tgt Cys		720
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-		_				-					-		_	aag Lys	_	816
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		-			-		-				-		_	aaa Lys	-	912
_	_	-			_		-	_	_			-		aag Lys		960
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				245					250					255		
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Lys	Asn	Val 275	Ile	Thr	Gln	Trp	G1u 280	Ala	Lys	Tyr	Lys	G1u 285	Val	Lys	Ala	
Arg	Asn 290	Ala	Gln	Leu	Leu	Lys 295	Met	Leu	Gln	Glu	Gly 300	Glu	Met	Lys	Asp	
Lys 305	Ala	Glu	Ile	Leu	Leu 310	Gln	Val	Asp	Glu	Ser 315	Gln	Ser	Ile	Lys	Asn 320	
G1u	Leu	Thr	Пe	G1n 325	Val	Thr	Ser	Leu	His 330	Ala	Ala	Leu	Glu	G1n 335	Glu	
Arg	Ser	Lys	Val 340	Lys	Val	Leu	Gln	A1a 345	Glu	Leu	Ala	Lys	Tyr 350	Gln	Gly	
Gly	Arg	Lys 355	Gly	Lys	Arg	Asn	Ser 3 <u>6</u> 0	Glu	Ser	Asp	Gln	Cys 365	Arg			
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	_						-	-	_		_			ttg Leu		144
									_	-		-		ctg Leu		192
-			-				-					_	aaa Lys	cag Gln		240

65					70					75					80		
-				-	-	aaa Lys										28	38
		-	-		-	tgt Cys					-			-		30	36
						aat Asn										38	34
-	-					aac Asn 135	-	_	-	-	-	_	-			43	32
				_	_	aaa Lys	-						-		,	48	30
	_		_			caa Gln		-			_		_	-		52	28
					_	cag Gln	-			-		_				57	'6
						ttg Leu							_		_	62	<u>?</u> 4
-			-			aaa Lys 215	_	-	-					-	-	67	'2
-			_	-	_	act Thr	_	_			_			_	_	72	20
	-	-	_			aga Arg	_			_			_			76	8

448

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235

Phe Glu Asp Lys Trp Phe Arg Lys Ile Lys Asp His Phe Cys Pro Phe

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	-	-	gga Gly	-			_			-	-						192
I.		Leu	gac Asp	Pro	Ser	Thr	Ala	Ser	Pro	Lys		Asn	Tyr	Thr			240
			caa Gln		_		-	-								-	288
			cat His	_		-		_			-,		-			-	336
			gca Ala		-			_	-						-	-	384

		115					120					125				
caa Gln					-					-		-	_	gtg Val		432
			-				_		-				_	tcc Ser		480
cgc Arg					-	-	_		-	_	_			•		528
ttc Phe					_			-							-	576
gct Ala												_			_	624
agc Ser																672
ggt Gly 225			_		_								-			720
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gaa Glu	-	-	-	_									taa *		,	810

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-	_			-		gcc Ala 55	-	-		-	-	-		-		192
						gct Ala										240
	_				-	agc Ser		_				_	_			288
-	_	-	-	_	_	act Thr		_	-	_	-	-		_		336
-	_	_		-		cga Arg	_	-	_		_	-				384
					-	att Ile 135			_				_			432
-				_		cgc Arg		_	_	_	-	-		_	-	480
						gct Ala										528

				165			•		170					175		
-			-		-	att Ile										576
_				-	-	gaa Glu		-	-					_		624
_			-			tcc Ser 215							-			672
-	_	_	_	-		ctg Leu							-	-	_	72 <u>(</u>
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Lys	Thr	A1a 35		Leu	Asp	Tyr	Ile 40	Lys	Arg	Cys	Arg	Pro 45		Asp	Ser	
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Leu	Leu	Leu	Lys 100	Ala	Leu	Thr	Leu	Met 105	Leu	Asp	Ala	Ala	Glu 110	Ser	Tyr	
Ala	Lys	Asp 115	Ser	Cys	Val	Arg	Gln 120	Ala	Gln	His	Cys	Gln 125	Arg	Leu	Thr	
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Leu	Pro	Arg	Phe	Tyr 165	Gln	Ala	Ser	Ile	Val 170	Ala	Glu	Ala	Tyr	Asp 175	Phe	
Val	Pro	Asp	Trp 180	Ala	Glu	Ile	Leu	Tyr 185	Gln	Gln	Val	Ile	Leu 190	Lys	Gly	
Asp	Phe	Asn 195	Tyr	Leu	Glu	Glu	Phe 200	Lys	Gln	Gln	Arg	Leu 205	Leu	Lys	Ser	
Ser	Ile 210	Phe	Glu	Glu	Ile	Ser 215	Lys	Lys	Tyr	Lys	G1n 220	His	Gln	Pro	Thr	
Asp 225	Met	Val	Met	Glu	Asn 230	Leu	Lys	Lys	Leu	Leu 235	Thr	Tyr	Cys	Glu	Asp 240	
Val	Tyr	Leu	Tyr	Tyr 245	Lys	Leu	Ala	Tyr	G1u 250	His	Lys	Phe	Tyr	G1u 255	Ile	
Val	Asn	Val	Leu 260	Leu	Lys	Asp	Pro	G1n 265	Thr	Gly	Cys	Cys	Leu 270	Lys	Asp	
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	ctt Leu				_	_	_				-	_	-	-	-	144
	aaa Lys 50		_		-	_					-				-	192
-	gag Glu	_	-	-		_	-			-						240
	aaa Lys	_	_		_	-							_		-	288
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Gln	Leu	Tyr 35		Ser	Leu	Met	Ala 40		His	Ala	Ser	Arg 45		Arg	Val	
Ile	Lys 50		Cys	Ile	Ala	G1n 55	_	Ser	Ala	۷al	Va1 60	. –	Asn	Leu	Arg	
Glu	Glu	Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	Gln	Leu	

65					70					75					80	
Arg	Lys	Glu	Gln	Thr 85	Lys	Leu	Lys	Trp	Met 90	Gln	Ser	Glu	Leu	Asn 95	Val	
Glu	Glu	Val	Val 100	Asn	Asp	Arg	Ser	Trp 105	Lys	Val	Phe	Asn	Glu 110	Arg	Cys	
Arg	Ile	His 115	Phe	Lys	Pro	Pro	Lys 120	Asn	Glui							
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													ata Ile			192
	-			-	-	_	-	-	-	-	_	_	gct Ala			240
							-	-					ttt Phe	-		<u>.</u> 288
													999 Gly		-	336

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	aat Asn									• •		_		-		384
	cat His 130															432
	tcg Ser				-							_		-	_	480
	cta Leu			_		_				_		-				528
	cac His	_		_		tga *										549
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Met	Gln	Arg 35		Ser	Leu	Arg	Phe 40		Gly	Pro	Met	Thr 45		Ser	Tyr	
Arg	Ser 50		Ala	Arg	Thr	Gly 55		Pro	Arg	Lys	Thr 60		Ile	Пе	Leu	
	Asp	Glu	Asn	Asp			Ala	Asp	Ala	-		Leu	Ala	Gly		
65 41 a	Ala	Ala	Glu	Leu 85	70 Leu	Ala	Ala	Thr	Va1 90	75 Ser	Thr	Gly	Phe	Ser 95	80 Arg	
Ser	Ser	Ala	Ile 100		Glu	Glu	Asp	Gly 105		Ser	Glu	Glu	Gly 110		Val	
Ile	Asn	Ala		Ala	Leu	Gly	Pro		Ala	Leu	Pro	Leu		Val	Gly	

		115					120					125				
His	His 130	Glu	Pro	Glu	Pro	Val 135	Trp	Glu	Ala	Ala	Arg 140	Pro	Phe	Arg	Ala	
Pro 145	Ser	Ser	Trp	Gly	Ala 150	Glu	Pro	Ala	Pro	His 155	Gly	Ala	Gln	Ala	Leu 160	
His	Leu	Ser	Thr	Met 165	Ser	Leu	Gln	Pro	Thr 170		Gly	Arg	Val	Pro 175		
Gly	His	Lys	Ser 180		Tyr											
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					.C 01	r G										
		100>														
								acc Thr								48
								ctg								96
ыу	Leu	Pro	20	Ald	rrp	GIY	Lys	Leu 25	Ald	Inr	Pne	ASN	30	irp.	ıyr	٠
								aat								144
Leu	rne	35	zer.	VdI	Ald	Pne	40	Asn	Ald	ASP	Ald	45	arg	arg	ınr	
								tgc					_			192
cys ·	50	uin	Leu	ınr	ınr	55	ыу	Cys	H15	ыу	5er	ыу	uin	Leu	ser	
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Lys 65	GIN	val	۲ro	val	Va I 70	5er	Ser	Ala	val	*						

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Leu Phe Asn Ser Val Ala Phe Gln Asn Ala Asp Ala Thr Arg Arg Thr
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Cys Pro Gln Leu Thr Thr Tyr Gly Cys His Gly Ser Gly Gln Leu Ser
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                                     10
                                                          15
ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
             20
gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
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Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
         35
                             40
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	cta Leu 50				-					_	-		_			19	12
	cga Arg												_		_	24	.0
	gag Glu													-		28	8
	aag Lys	-		-	-		-	_						_	•	33	6
-	gat Asp		_			_			-	_			-			38	,4
	tgg Trp 130															43	.2
	ccc Pro												_	_	-	48	0
	tgc Cys			_	_	_				_	-	-	-			52	8
	ggc Gly															57	6
	ggc Gly															62	4
	agg Arg 210															67	2

		_	gcc Ala		_				-	_	-		-	720
			tac Tyr 245										_	768
_		_	ggç Gly			-			_				_	816
-	,		agc Ser		_	-	_	-		-			gag Glu	864
-	-		gat Asp	_	-			-				_	-	912
			aga Arg		_	-	_					-		960
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Phe	Leu 50	Glu	Gln	Arg	Leu	Pro 55	Glu	Ile	Asn	Leu	Asp 60	Gly	Met	Val	Gly
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Gln	Glu	Pro	Leu	Leu 85	Gln	Pro	Leu	Ser	Leu 90	Arg	Val	Gly	Met	Leu 95	Gly
	-		100					105					Leu 110	•	
Ser	Asp	Pro 115	Lys	Tyr	Leu	Arg	Glu 120	Phe	Gln	Leu	Thr	Leu 125	Gln	Pro	Gly
	130	-				135	·				140		Ser		
145				•	150		•			155			Arg		160
				165					170		•		Ser	175	
			180	·				185					Pro 190		_
		195					200					205	Trp		
	210	-				215					220		Asp	•	
225					230					235			Ala		240
				245			_	Ť	250				Asn	255	
			260					265					Arg 270		
		275					280					285	Phe		
	290					295					300		Tyr		
His 305	Phe	Ser	Arg	Arg	Val 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	G1'y 320
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Leu	Tyr	Ile	Leu 340	Ala	Glu	Tyr	Pro	Pro 345	Ala	Asn	Arg	Glu	Pro 350	His	Pro

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					aag Lys										192
					gag Glu 70							_		_	240
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					gag Glu										336

					ctc Leu								_			384
	_	_			aac Asn		-	-			_	_		_		432
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-					gag Glu	-		-	-	Leu			-			528
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	-		-		cct Pro		-	-		-		_				624
		_	-	_	cag Gln									-	-	672
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					ggc Gly											768
-		_	_		gac Asp	-		_					_			816
_		_			ctg Leu			_					_			864

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					gcc Ala 310								-	_		960
	-	-	_	-	cgg Arg	_							_	_	_	1008
		_	_	-	aag Lys	-					_	_			_	1056
	-		-	-	cgt Arg	-		_	_			-	_	_		1104
_					gtg Val	-	-	-		-	_	•				1152
			-		ctt Leu 390	_		_	_	_					~ ~	1200
	_			-	cct Pro					_				-	•	1248
_	_				tct Ser			_	-		_			-		1296
					ctg Leu											1344
Gly					ctc Leu											1392

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Phe	Leu	Thr	Phe	Pro 245	Gly	Leu	Arg	Leu	Ala 250	Gln	Thr	His	Arg	Asp 255	
Leu	Thr	Met	Ser 260		Asp	Arg	Pro	Met 265		Gln	Phe	Leu	Leu 270		Thr
Ser	Phe	Leu 275	Ser	Pro	Leu	Phe	Ile 280	Leu	Trp	Leu	Trp	Thr 285	Lys	Pro	Ile
Ala	Arg ⁻ 290	Asp	Phe	Leu	His	G1n 295	Pro	Pro	Phe	Gly	G1u 300	Thr	Arg	Phe	Ser
Leu 305	Leu	Ser	Asp	Ser	Ala 310	Phe	Asp	Ser	Gly	Arg 315	Leu	Trp	Leu	Leu	Val 320
Val	Leu	Cys	Leu	Leu 325	Arg	Leu	Ala	Val	Thr 330	Arg	Pro	His	Leu	G1n 335	Ala
Tyr	Leu	Cys	Leu 340	Ala	Lys	Ala	Arg	Val 345	Glu	Gln	Leu	Arg	Arg 350	Glu	Ala
Gly	Arg	11e 355	Glu	Ala	Arg	Glu	Ile 360	Gln	Gln	Arg	Val	Val 365	Arg	Va1	Tyr
Cys	Tyr 370	Val	Thr	Val	Val	Ser 375	Leu	Gln	Tyr	Leu	Thr 380	Pro	Leu	Ile	Leu
Thr 385	Leu	Asn	Cys	Thr	Leu 390	Leu	Leu	Lys	Thr	Leu 395	Gly	Gly	Tyr	Ser	Trp 400
Gly	Leu	Gly	Pro	Ala 405	Pro	Leu	Leu	Ser	Pro 410	Asp	Pro	Ser	Ser	Ala 415	Ser
Ala	Ala	Pro	Ile 420	Gly	Ser	Gly	Glu	Asp 425	Glu	Val	Xaa	Gln	Thr 430	Ala	Ala
Arg	He	A1a 435	Gly	Ala	Leu	Gly	G1y 440	Leu	Leu	Thr	Pro	Leu 445	Phe	Leu	Arg
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Lys		Leu 35		Thr	Tyr	Pro	Lys 40		Ala	Gly	Glu	Met 45		Glu	Asp	
Gly			Arg	Phe	Leu	Cys 55		Ser	Val	Phe	Ser		Gln	Val	Ala	

Ser Thr Leu Lys Gln Val Lys His Asp Gln Gln Val Ala Arg Met Glu

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Lys	Pro	Ile	Glu 100		Leu	Leu	Gly	Phe 105		Pro	Ser	Ser	Gly 110			
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						act Thr										240
						tac Tyr					_				-	288

					aca Thr						-			336
					gta Val					-		-		384
-	_				cct Pro 135									432
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	_				cca Pro	_		-	-	-	_			576
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4.71

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		-		-					-		_			gtc Val		1152
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		He										-	_	tcc Ser		1296
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472

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                            40
                                                45
Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
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Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
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Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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210

.215

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	Gly	Leu	Ser	G1n 245		Met	Lys	Leu	Pro 250		Pro	Ala	His	His 255	
Trp	Ser	Leu	Leu 260	Ser	G1u	Ala	Thr	G1y 265	Lys	Ile	Phe	Asp	Leu 270	Leu	Pro
Asn	Lys	I1e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Пe	Ser 285	Ile	Ala	Lys
	290					295		Ţ			300			Gln	
305					310					315	-			Leu	320
		•		325					330		·			Arg 335	
			340			·		345					350	Leu	
		355			·		360	·				365	•	Pro	
	370					375	•				380		•	Val	
385					390		•			395				Leu	400
	-			405					410				•	Trp 415	
			420					425					430	Ser	
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	-	_					_						agt Ser	_	tta Leu 240	. 720
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								Asn					ctg Leu			1008
-		-											att Ile 350			1056

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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
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Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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                                                125
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Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265		Ile	Phe	Asp	Leu 270	Leu	Pro
Asn	Lys	I1e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Ile	Ser 285	Пe	Ala	Lys
Cys	Leu 290	Leu	Glu	Met	Thr	Asp 295	Asp	Asp	Ala	Asn	Arg 300	Ile	Ala	Gln	Val
Thr 305	Ĺys	Ser	Asn	Пe	Glu 310	Lys	Ala	Ala	Phe	Val 315	Lys	Leu	Tyr	Leu	Val 320
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Asp	Phe	Phe	Leu	Leu 405	He	Phe	Ala	Thr	Ala 410	Val	Val	Ala	Trp	Ala 415	Asp
His	Thr	Ala	Pro 420	Leu	Leu	Leu	Gly	Leu 425	Ser	Ala	Ser	Trp	Leu 430	Pro	Trp
His	Gln	G1u 435	Asn	Gly	Pro	Ala	Gly 440	Pro	Val	Pro	Ser	Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	G1n	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
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480

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														ttc Phe 175		528
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Ala	Val	Va1 35	Arg		_	Phe		Ser	Thr	Ala		G1u 45		Thr	Leu	
Ser	Arg 50								Arg	Arg			Glu	Tyr	Asp	
His		Asp	Ala	Ala	Пe		Gly	Phe	Arg	Glu		Glu	Lys	Ser	Arg	
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Trp	Ser	Glu	Ala	Ser 85	Arg	Ala	He	Leu	G1n 90	Arg	Val	Gln	Ala	Ala 95	Ala	
Phe	Gly	Pro	Gly 100		Thr	Leu	Leu	Ser 105		Val	His	Val	Leu 110	Asp	Leu	
Glu	Ala	Arg 115		Tyr	Ile	Lys	Pro 120		Val	Asp	Ser	Ile 125		Phe	Cys	
Glv	د [۸		Πο	د ۲۸	Glv	l Au		Lou	Lou	Sor	Dro		Val	Mot	Ara	

Gly Ala Thr Ile Ala Gly Leu Ser Leu Leu Ser Pro Ser Val Met Arg

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Pro	Gly	Ser	Leu	Tyr 165	Ile	Leu	Arg	Gly	Ser 170	Ala	Arg	Tyr	Asp	Phe 175	Ser	
His	Glu	Ile	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
Pro	Arg	Gly 195	Arg	Arg	Ile	Ser	Val 200	Ile	Cys	Arg	Ser	Leu 205	Pro	Glu	Gly	
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Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Glu Met Pro Gln 35 40 45

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 50 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 65 70 75 . 80

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1 5 10 15

ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg 96 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

483

20 25 30

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tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg 192 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 55

ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag 240 Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 75

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Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala

Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 55

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Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln

75

70

cag ggt tct ttg taa Gln Gly Ser Leu *

65

255

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485

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Ala	Met	A1 a 35	Lys	Met	Ser	Lys	Va1 40	Gly	Lys	Val	Val	Phe 45		Arg	Leu		
Gln	Asp 50	Lys	Lys	Tyr	Tyr	Asp 55	Lys	Lys	Tyr	Gln	Va1 60	Phe	Leu	Lys	Leu		
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	aca Thr						-		-			_	-			240)

65					70					75					80	
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		cgg Arg 115					_	-		-				-	_	384
-	-	aaa Lys	_						_	-						432
-	-	gat Asp	_		-		-	_	-		-	_	-	٠,		480
		cgg Arg														528
	-	cct Pro										tga *				567
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Gln	Thr	His 35	20 Lys	Tyr	Ala	Pro	Phe 40	25 Ile	Пе	He	Gly	Leu 45	30 His	Leu	Ala	
Leu	Gly	Ile	Phe	Ser	Phe	Thr		Asp	Thr	Trp	Ser		Ser	Arg	Gly	

	50					55					60					
Asp 65	Thr	Ala	Glu	Ile	Leu 70	Gly	Ser	Gly	Ala	Gly 75	Ile	Ala	Cys	Gly	Ser 80	
His	Val	Thr	Tyr	Asn 85	Met	Gly	Leu	Val	Leu 90	Asp	Pro	Ser	Leu	Asp 95		
Leu	Pro	Leu	Ala 100	Gly	Pro	Pro	Ile	Thr 105	۷al	Thr	Leu	Phe	Gly 110	Lys	Ala	
Ile	Leu	Arg 115	Ile	Leu	Пe	Gly	Met 120	Val	Phe	Val	Leu	Ile 125	Ile	Arg	Asp	
Val	Met 130	Lys	Lys	Ile	Thr	Ile 135	Pro	Leu	Ala	Cys	Lys 140	Ile	Phe	Asn	Ile	
Pro 145	Ċys	Asp	Asp	Ile	Arg 150	Lys	Ala	Arg	Gln	His 155	Met	Glu	Val	Glu	Leu 160	
Pro	Tyr	Arg	Tyr	Ile 165	Thr	Tyr	Gly	Met	Val 170	Gly	Phe	Ser	Ile	Thr 175	Phe	
Phe	Val		Tyr 180	Ile	Phe	Phe	Phe	Ile 185	Gly	Ile	Ser					
	<2 <2	210> 211> 212> 21 <u>3</u> >	210	o sap	oiens	5										
	<2	220> 221> 222>	CDS (1).	(2	210)											
at a		100>		++0	ata.	000	tot	cto	aat	atc	cta	tat	++0	ctt	cta	48
							tct Ser									40
							tgc Cys									96
							gcg Ala 40									144
							tgg Trp									192

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tac cta acc att ctt taa
                                                                      210
Tyr Leu Thr Ile Leu *
 65
      <210> 340
      <211> 69
      <212> PRT
      <213> Homo sapiens
      <400> 340
Met Val Ser His Phe Met Gly Ser Leu Ser Val Leu Cys Phe Leu Leu
                 5
                                    10
Leu Leu Gly Phe Gln Phe Val Cys Pro Gln Pro Ser Thr Gln His Arg
                                25
Lys Val Pro Gln Arg Met Ala Ala Glu Gly Ala Pro Glu Asp Asp Gly
                            40
Gly Gly Gly Ala Pro Gly Val Trp Gly Ala Gly Ala Pro Ala Glu Gly
                        55
                                            60
Tyr Leu Thr Ile Leu
65
      <210> 341
      <211> 225
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(225)
      <400> 341
atg ccg gct aag gac aca agt tca gtg ttt gcc ctg gct tgt agc cca
                                                                       48
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
1
                 5
                                     10
gcg ggg gct ccg tca tcc cct ggg gaa tgc ctc ggc ctg caa gac cgc
                                                                       96
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
             20
                                 25
                                                     30
ata ccg cat tgg aac agg gaa acc acc tac ttc agc acc tcc ctc agc
                                                                      144
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
         35
                             40
                                                 45
```

```
aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg
                                                                      192
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
     50
                         55
                                              60
cat tcg gga tat ggc tcc ctg gcc agc ttg tga
                                                                      225
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu *
 65
                     70
      <210> 342
      <211> 74
      <212> PRT
      <213> Homo sapiens
      <400> 342
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
                 5
                                    10
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
                                25
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu
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atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc
                                                                       48
Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu
1
                 5
                                     10
                                                         15
atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca
                                                                       96
Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr
             20
                                 25
```

492

ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 45 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 55 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile * 70 65 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 10 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 55 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 65 70 75 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg 48 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 10 15

493

								-			_	agg Arg		96
	_					 _			_		_	ccc Pro		144
						-	-		_		-	aac Asn		192
					-			_		_	_	act Thr		240
_		_	-	gat Asp	_		-			_	-	taa *	;	285
_^	210~	216												

<210> 346

<211> 94

<212> PRT

<213> Homo sapiens

<400> 346

 Met
 Thr
 Ala
 Lys
 Asp
 Cys
 Ser
 Ile
 Met
 Ile
 Ala
 Leu
 Ser
 Pro
 Cys
 Leu

 Gln
 Asp
 Ala
 Ser
 Ser
 Asp
 Gln
 Arg
 Pro
 Val
 Val
 Pro
 Ser
 Ser
 Arg
 Ser
 Asp
 Leu
 Asp
 Leu
 Asp
 Leu
 90

<210> 347

<211> 474

<212> DNA

<213> Homo sapiens

	<	220> 221> 222>		(4	474)											
	gag Glu		ctg										_	_	_	48
-	agg Arg	_		_	_	•	-	-	_	-		_		-	•	96
	gag Glu		-	-			_	_	_		-	-	_			144
	tcc Ser 50		-				-	_	_	_		_	_			192
	tcg Ser														_	240
-	acc Thr		-					_			-		_	_		288
	cag Gln	-	-	-		-		_	Phe		_			_	-	336
-	aac Asn															384
	gcc Ala 130	-	_							-						432
	tat Tyr															474

495

145 150 155 <210> 348 <211> 157 <212> PRT <213> Homo sapiens <400> 348 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu 10 Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala 25 Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly 55 Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu 70 75 Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro 90 Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 105 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 115 120 125 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 135 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 145 150 <210> 349 <211> 288 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(288)

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Met Ala Lys Ala Leu Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile
1 5 10 15

_		-	 _	-	_				aaa Lys		96
						 		-	gtg Val	•	144
									aac Asn	-	192
									aca Thr		240
				-					gtt Val 95	_	288

<210> 350

<211> 95

<212> PRT

<213> Homo sapiens

<400> 350

 Met Ala Lys Ala Leu Ile Val Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile 1
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90

95

<210> 351

<211> 165

<212> DNA

<213> Homo sapiens

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      <221> CDS
      <222> (1)...(165)
      <400> 351
atg tgc tcc atc ccc cgg cat ctg ctg cca ttg gtc ctg cct gtt gcg
                                                                      48
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
1
                 5
                                     10
tta ctt ctc tgt gcc ctg gag ccc ctc aag cac aga ggc ctc gaa agg
                                                                      96
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
ttg atc aga cat cct cag cac ctg gag cgg ggc ctg gca cac aag acg
                                                                     144
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
         35
                             40
                                                 45
gca atg aac ggc caa ccc tag
                                                                     165
Ala Met Asn Gly Gln Pro *
     50
      <210> 352
      <211> 54
      <212> PRT
      <213> Homo sapiens
      <400> 352
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
. 1
                                    10
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
            20
                                25
                                                    30
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
                            40
Ala Met Asn Gly Gln Pro
    50
      <210> 353
      <211> 159
      <212> DNA
      <213> Homo sapiens
      <220>
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<221> CDS
      <222> (1)...(159)
      <400> 353
atg tgc ttg agg gtt ttc acc ctg gcc ctc agt tgc ctg tgc ggg
                                                                      48
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                                     10
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                      96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                 25
             20
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
                                                                     144
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
                             40
                                                 45
cgt gtc ggg ctt tga
                                                                     159
Arg Val Gly Leu *
     50
      <210> 354
      <211> 52
      <212> PRT
      <213> Homo sapiens
      <400> 354
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                5
                                   10
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                25
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
       35
                            40
                                                45
Arg Val Gly Leu
    50
      <210> 355
      <211> 210
      <212> DNA
     <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(210)
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-	ggt	_	atg			gat Asp				-		_	_		_		48
				- •	-	tac Tyr		-				-					96
						tgt Cys											144
-		-	-		_	gaa Glu 55					_			_			192
	gaa Glu				tag *												210
	<2 <2	210> 211> 212> 213>	69	o sap	oiens	5		٠									
	<4	100>	356														
Met 1	Gly	Ala	Met	Asn 5	His	Asp	Thr	Asn	Tyr 10	Ser	Phe	Gln	Val	Gln 15	Cys		
_	Leu	Ile	Va1 20	-	Ala	Tyr	Lys	Asp 25		Ser	Pro	Ala	His 30		His	٠	
Phe	Met	Asp 35		Glu	Leu	Cys	Ser 40		Tyr	Trp	Thr	Lys 45		Leu	Leu		
Arg	Leu 50		Glu	Tyr	Thr	G1u 55	Lys	Lys	Lys	Asn	G1n 60	Asn	Ile	Gln	Lys		
Pro 65	Glu	Tyr	Ser	Glu		3.5		•									
		210> 211>															

<212> DNA

<213> Homo sapiens

PCT/US00/29052

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atg gtc ctg ccg gtg gca gcc tat ggn ctg atc ctg atg gcc atg ctg
                                                                       48
Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
1
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                       96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
             20
                                 25
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
                             40
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                         55
                                             60
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
                                                                      240
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
65
                     70
                                         75
                                                                      243
tga
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<210> 358
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<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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<223> Xaa = Any Amino Acid

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Met 1	Val	Leu	Pro	Val 5	Ala	Ala	Tyr	Xaa	Leu 10	Ile	Leu	Met	Ala	Met 15	Leu	
Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Ala	Gly	Trp	Gly	A1a 30	Leu	Leu	
Phe	Thr	Leu 35	Ser	Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45	Ala	Gln	Pro	
Leu	Pro 50	His	Ala	Arg	Leu	Va1 55	Ile	Met	Thr	Thr	Tyr 60	Tyr	Ala,	Ala	Gln	
Leu 65	Leu	Ile	Thr	Leu	Ser 70	Ala	Leu	Arg	Ser	Pro 75	Val	Pro	Lys	Thr	Asp 80	
	<2	?10> ?11>	324													
		?12> ?13>		sap	oiens	5										
	<2	220> 221> 222>		(3	324)											
		100>			,											
	aag Lys	agc	acc													48
	gca Ala		-	-	-	-	-		-			-			_	96
	ccg Pro.			-								-		_		144
-	cga Arg 50												-	_		192
	gcc Ala		-			_									-	240
aqt	taa	qca	gga	aga	ctc	att	ctq	aqt	qta	gat	ggc	tct	ggg	ttt	tat	288

```
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                                     90
                                                         95
                                                                     324
gag agg gtg aaa tct ttg gtc gtt aaa caa ttc tag
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
                 5
                                    10
Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
                        55
                                            60
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
                    70
                                       75
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                                    90
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
      <210> 361
      <211> 252
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(252)
      <400> 361
atg gag gaa gga ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
                                                                      48
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                 5
                                     10
                                                         15
                                                                      96
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
```

503

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg	
-					agc Ser	-	-				-	-				144
					ctg Leu					-				_	_	192
		-		-	aca Thr 70		-			-						240
	aaa Lys	aac Asn	taa *					•								252

<210> 362

<211> 83

<212> PRT

<213> Homo sapiens

<400> 362

<210> 363

Lys Lys Asn

<211> 459

<212> DNA

<213> Homo sapiens

504

<220> <221> CDS <222> (1)...(459) -<400> 363 atg gat gga aca caa cag cag att ttt aaa atg tta gca gag gta cta 48 Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu 1 5 10 15 gga gga atc aat tgt gta aaa gcc tcg gtt ctt acg cct tat tac cac 96 Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His 20 25 aaa gta gat ttt gag tgt atc ttg gat aaa aga aaa aaa cct ctt ccg 144 Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro 35 40 tat gga agc cat aat ata gca ttg gga caa cta cca gaa atg ccc tgg 192 Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp 50 55 60 gaa toa aat ato gaa ata gtt gga toa agg ctg coa coa ggg got gaa 240 Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu 65 70 agg att gct ttg gaa ttt ttg gat tca aaa gca ctt tgt aga aat atc 288 Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile 85 90 95 cct cac atg aaa gga aaa tct gct atg aaa aaa cga cat ttg gaa att 336 Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile 100 105 ctg ggg tat cgt gta att cag att tcc cag ttt gaa tgg aac tct atq 384 Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met 115 120 125 gca ctg tca aca aag gat gct cgg atg gac tac ctg aga gaa tgt ata 432 Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile 130 135 140 ttt gga gaa gtc aag tca tgt ttg tag 459 Phe Gly Glu Val Lys Ser Cys Leu * 145 150

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<210> 364
      <211> 152
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      <400> 364
Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu
                                    10
Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
                                25
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro
                            40
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
                                105
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
                                                125
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
                        135
Phe Gly Glu Val Lys Ser Cys Leu
145
                    150
      <210> 365
      <211> 600
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(600)
      <400> 365
atg gtg tgg cgc cgg ctt ctg cgg aag agg tgg gtg ctc gcc ctg gtc
                                                                       48
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
1
                 5
                                     10
                                                         15
ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
                                                                       96
```

Phe	Gly	Leu	Ser 20	Leu	Val	Ţyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	Glu	
				_	-					-	-		-	cat His		144
_			-							_			-	agt Ser	•	192
-	-		_	_	-	Asn					_			atc Ile	-	240
_	_				_	_			_	-	_	_	-	aat Asn 95		288
			_		_					_		-	_	gat Asp		336
_					-	_	_	_				_	_	tcc Ser	-	384
	_	_			_				_		-			aac Asn		432
														cac His		480
	-	-	-	-		-					_	_		cag Gln 175		528
									Lys					gaa Glu	-	576
ccg	ССС	gag	ctc	ttc	ссс	gct	tga									600

```
Pro Pro Glu Leu Phe Pro Ala *
        195
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      <211> 199
      <212> PRT
      <213> Homo sapiens
      <400> 366
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
                                    10
Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
                                25
Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                               105
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                            120
Cys Leu Gin Pro Asn Lys Gin Leu Leu Leu Glu Arg Phe Leu Asn Arg
                       135
                                            140
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
145
                    150
                                        155
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
                                    170
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
           180
                                185
                                                    190
Pro Pro Glu Leu Phe Pro Ala
       195
      <210> 367
      <211> 249
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
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508

<222> (1)...(249)

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<210> 368

<211> 82

Ser Gly *

<212> PRT

<213> Homo sapiens

<400> 368

 Met Ser Lys
 Tyr Lys
 His Lys
 Ser Ser Pro Leu Leu Leu Pro Leu Leu Ile

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 10
 15

 Phe His Asn Val Cys
 Phe Ser Pro Ala Asn Lys
 Pro Lys
 Ile Leu Ala 30

 Asn Glu Lys
 Val Ile Thr Val Leu Ala Ala Cys
 Leu Glu Ser Glu Asn 40
 Ser Asp Leu Gln 50

 Gln Asn Ala Gln Arg
 Ile Gly Ala Ala Ala Leu Gly
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 Leu Ser Glu Gly
 Lys
 Asn Ser Phe Glu Lys
 Pro Ile Ser Lys
 Lys
 Lys

 65
 70
 75
 80

509

Ser Gly

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<210> 370

<211> 94

<212> PRT

<213> Homo sapiens

<400> 370

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Pro	Pro	A1 a 35	Pro	Gln	Asn	Pro	Gly 40	Gly	Ser	Thr	Gln	Ala 45	Pro	Gln	Arg	
Val	Val 50	Gly	Lys	Ser	His	Ser 55	Gly	Ile	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
Asn 65	Leu	Arg	Leu	Glu	Ser 70	Lys	Leu	Asn	Arg	Thr 75	Ala	Val	Cys _.	Glu	A1a 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 90	Gly	Val	Gly	Ser			
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			-		_								gac Asp	-	-	144
				-		-						_	gag Glu	-	-	192 :
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511

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Pro Arg *
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 25
 30
 30

 Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35
 40
 45

 Val Asp Gln Ala Leu Trp Glu Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50
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 Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65
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 80

 Pro Arg

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<222> (1)...(219)

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96

nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc tca gcc cat Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His 20 25 30 512

tac gca aac ctg gcg ggt cca acc aac ccc gct ctg ccg ccg ctg ctg 144 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga 192 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly 50 55 aat acc acg cac tgc ccc ttc gcc tag 219 Asn Thr Thr His Cys Pro Phe Ala * 65 70 <210> 374 <211> 72 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(72) <223> Xaa = Any Amino Acid <400> 374 Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Ala Xaa Leu 1 5 10 Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Ser Ala His 25 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu 40 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly Asn Thr Thr His Cys Pro Phe Ala 65 70 <210> 375 <211> 579 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(579)

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•	_		_	-	•	-		_		_	-	•	_	gcc Ala		144
	-	_	=			-	_				-	-		gct Ala		192
-			-		-							_		gat Asp		240
					_	-			_		_		-	gga Gly 95		288
	_		_	-		_							-	ggc Gly	-	336
		_		_	-	_						_		atc Ile		. 384
	-	-	_											999 Gly		432
_	_			_										agg Arg		480
														gta Val		528

514

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
180
185
579

<210> 376 <211> 192 <212> PRT <213> Homo sapiens

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Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu

185

190

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515

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	agt Ser															480
	tac Tyr													-	-	528
	ctg Leu	_	-	_		_	-	-								576
	999 Gly								tga *							606
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1		Val	Gln Leu	5				Ala	10				Trp	15		
1 Ser	Thr	Val Ile Leu	Gln Leu 20	5 Asn	Asn	Val	Ala Arg	A1a 25	10 Phe	Thr	Ser	Asn Leu	Trp 30	15 Val	Cys	
1 Ser Gln	Thr Leu Thr Trp	Val Ile Leu 35	Gln Leu 20 Glu	5 Asn Asp	Asn Gly	Val Arg Thr	Ala Arg 40	Ala 25 Arg	10 Phe Ser	Thr Val	Ser Gly Ser	Asn Leu 45	Trp 30 Trp	15 Val Arg	Cys Ser	
1 Ser Gln Cys	Thr Leu Thr	Val Ile Leu 35 Leu	Gln Leu 20 Glu Val	5 Asn Asp Asp	Asn Gly Arg Ala	Val Arg Thr 55 His	Ala Arg 40 Arg	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu	Thr Val Pro Ala	Ser Gly Ser 60 Leu	Asn Leu 45 Pro Gly	Trp 30 Trp Gly	15 Val Arg Ala	Cys Ser Arg Ser	
1 Ser Gln Cys Ala 65	Thr Leu Thr Trp 50	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val	5 Asn Asp Asp Asp	Asn Gly Arg Ala 70	Val Arg Thr 55 His	Ala Arg 40 Arg	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu Gly	Thr Val Pro Ala 75	Ser Gly Ser 60 Leu	Asn Leu 45 Pro Gly	Trp 30 Trp Gly Trp	15 Val Arg Ala Gly Gln	Cys Ser Arg Ser 80	
1 Ser Gln Cys Ala 65 Glu	Thr Leu Thr Trp 50 Gly	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val Val Gly Arg	5 Asn Asp Asp Asp Phe 85	Asn Gly Arg Ala 70 Gln	Val Arg Thr 55 His Glu	Ala Arg 40 Arg Asp Ser	Ala 25 Arg Gly Cys Arg	10 Phe Ser Gly Glu Gly 90	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys	Trp 30 Trp Gly Trp Leu Leu	15 Val Arg Ala Gly Gln 95	Cys Ser Arg Ser 80 Phe	
1 Ser Gln Cys Ala 65 Glu Asp	Thr Leu Thr Trp 50 Gly Ala	Val Ile Leu 35 Leu Gln Ala Met Leu	Gln Leu 20 Glu Val Val Gly Arg 100	5 Asn Asp Asp Phe 85 Ala	Asn Gly Arg Ala 70 Gln Cys	Val Arg Thr 55 His Glu Asn	Ala Arg 40 Arg Asp Ser Leu Gly	Ala 25 Arg Gly Cys Arg Val 105	10 Phe Ser Gly Glu Gly 90 Ala	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys Ala Pro	Trp 30 Trp Gly Trp Leu Leu 110	15 Val Arg Ala Gly Gln 95 Thr	Cys Ser Arg Ser 80 Phe	
1 Ser Gln Cys Ala 65 Glu Asp	Thr Leu Thr Trp 50 Gly Ala Met Gln	Val Ile Leu 35 Leu Gln Ala Met Leu 115	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala	Asn Gly Arg Ala 70 Gln Cys Leu	Val Arg Thr 55 His Glu Asn Leu	Ala Arg 40 Arg Asp Ser Leu Gly 120	Ala 25 Arg Gly Cys Arg Val 105 Leu	10 Phe Ser Gly Glu Gly 90 Ala	Thr Val Pro Ala 75 Thr Thr	Ser Gly Ser 60 Leu Val Ala	Asn Leu 45 Pro Gly Lys Ala Pro 125	Trp 30 Trp Gly Trp Leu Leu 110 Leu	15 Val Arg Ala Gly Gln 95 Thr	Cys Ser Arg Ser 80 Phe Ala Ser	
1 Ser Gln Cys Ala 65 Glu Asp Gly Pro	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp 130	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe Cys	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu 135	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu	10 Phe Ser Gly Glu Gly 90 Ala Val	Thr Val Pro Ala 75 Thr Gly Ala	Ser Gly Ser 60 Leu Val Ala Leu Ala 140	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala	Trp 30 Trp Gly Trp Leu 110 Leu Phe	15 Val Arg Ala Gly Gln 95 Thr Leu Gln	Cys Ser Arg Ser 80 Phe Ala Ser Leu	
1 Ser Gln Cys Ala 65 Glu Asp Gly Pro	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe Cys Leu	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu 135	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu	10 Phe Ser Gly Glu Gly 90 Ala Val	Thr Val Pro Ala 75 Thr Gly Ala	Ser Gly Ser 60 Leu Val Ala Leu Ala 140	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala	Trp 30 Trp Gly Trp Leu 110 Leu Phe	15 Val Arg Ala Gly Gln 95 Thr Leu Gln	Cys Ser Arg Ser 80 Phe Ala Ser Leu	

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_		_	_		gcc Ala		_					-		_	96
	-			-	gga Gly							-	-		144
					gtc Val 55										192
					gag Glu										240
-	_	-			agc Ser	-				-					288

518

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Thr Gly *
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      <211> 98
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Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
                        55
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
                    70
                                        75
Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe Thr Glu
                                    90
                85
Thr Gly
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      <211> 264
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      <221> CDS
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Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
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10

15

1

	ttc Phe															96
	cca Pro										-					144
	agc Ser 50		_								-	_				192
	cgc Arg		_							_	_		-	_		240
	gga Gly					-	tga *									264
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Leu	Phe	Leu	Thr 20	Cys	Tyr	Ala	Asp	Asp 25	Lys	Pro	Asp	Lys	Pro 30		Asp	
Lys	Pro	Asp 35		Ser	Gly		Asp 40		Lys	Pro	Asp	Phe 45		Lys	Phe	
Leu	Ser 50		Leu	Gly	Thr		. •	IJе	Glu	Asn	Ala 60		Glu	Phe	Ile	
Leu 65	Arg	Ser	Met	Ser	Arg 70		Thr	Gly	Phe	Met 75		Phe	Asp	Asp		
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520

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Val Leu Pro Glu Gln Glu Thr Pro Arg Glu

70

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	gcc		ccg						-	_		-	ncg Xaa 15	_	48
													cgg Arg		96
												_	cca Pro	-	144
													gac Asp		192
													ctg Leu	_	240
-	-		_	_	-	_	_	_	_			999 Gly	cac His 95	tga *	288

<210> 386

<211> 95

<212> PRT

<213> Homo sapiens

522

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	50					55					60						
_			-	_	_	_								cta Leu			240
	_		-	-										tca Ser 95		2	288
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	ctt Leu		tgg Trp	tga *												3	351
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	Phe	Val	Phe 20		Gly	Asn	Ser	Ser 25		Ala	Pro	Gln	Arg 30	Leu	Leu		
Glu	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40	Ala	Met	Leu	Tyr	Leu 45	Lys	Gly	Ala		
Gln	Gly 50	Arg	Arg	Phe	Ile	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser		
Asp 65		Pro	Leu	Pro	G1u 70		Arg	Ser	Pro	Asn 75		Gln	Leu	Leu	Thr 80		
	Pro	Glu	Ala	Ala 85		Ile	Leu	Leu	A1a 90		Leu	Gln	Lys	Ser 95			
	Asp Leu		100		Asn	Phe	Asp	Gln 105		Arg	Phe	Leu	Glu 110	Asp	Ser		
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524

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<210> 390

<211> 105

<212> PRT

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Asp	Phe	Lys 35	Tyr	Ala	Leu	Ile	Gly 40	Thr	Ala	Val	Gly	Va1 45	Ala	Ile	Ser	
Ala	G7у 50	Phe	Leu	Ala	Leu	Lys 55	Ile	Cys	Met	Пe	Arg 60	Arg	His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70	Leu	Lys	Ser	Thr	Pro 75	Gly	Gly	Leu	Ser	Asp 80	
Thr	Ile	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95	Ser	
Lys	Arg	Asp	Ala 100	Gln	Val	Ile	Glu	Leu 105					,			
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	<2	220> 221> 222>		(.	150)											
	<2	222>	(1)	(1	ature 150) .C oi											
_	gcc		ctc	-	gtc Val							-	-	-	-	48
					gtc Val											96
					cct Pro											144
gcc Ala	taa *														٠	150

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<210> 392

526

PCT/US00/29052

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            20
Thr Gln Asp Gly Lys Pro Glu Arg Ile Ala Gln Leu Thr Trp Asn Glu
                            40
Ala
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Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Leu
 1
                                     10
                                                                       96
ccc cag gag cag ata cag gcc gag ctg agc ccc gcc cat gac cgt cgc
Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg
             20
                                 25
                                                     30
cca ctg cca ggt ggg gac gag gcc atc act gcc atc tgg gag acc cgg
                                                                      144
Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg
         35
                             40
                                                 45
cta aag gcc caa ccc tgg ctc ttc gac gcc ccc aag ttc cgc ctg cac
                                                                      192
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527

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 60 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 70 75 65 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 294 ttc tga Phe * <210> 394 <211> 97 <212> PRT <213> Homo sapiens <400> 394 Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu 5 10 Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg 25 Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 55 60 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu 75 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 90 Phe <210> 395 <211> 303 <212> DNA

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<220> <221> CDS

528

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35

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40

529

Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser 50 55 Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile 70 75 Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met 90 -85 Glu Asn Glu Thr 100 <210> 397 <211> 141 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(141) <400> 397 48 Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn 1 5 10 15 ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg 96 Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu 25 20 gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga 141 Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu * 35 40 45 <210> 398 <211> 46 <212> PRT <213> Homo sapiens <400> 398 Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn 5 10 Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu 25 Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu 35 40 45

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_	cag	-	agc		-		-		cct Pro 10		-	_		-	48
		_	-						cta Leu			_		_	96
				_				_	agc Ser	_		-		-	144
			_						aac Asn			-	_		192
	_			_		_	_		cct Pro				_		240
					-		-		ccc Pro 90						288
									gac Asp						336
	gta Val						tga *								360

531

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		_	_		-	aaa Lys 55	-	-					-				192
						cat His											240
		-	-			aat Asn				_			_				288
		-				gct Ala					_	_	-				336
						aat Asn											384
			_			aac Asn 135		_	_					-	-		432
			-	-		tac Tyr				-			tag *				474
	<2 <2	210> 211> 212> 213>	157	sap	oiens	ŝ											
Mo+		100>		Cuc	G1v	Acn	Acn	Ĺou	۸٦٥	۸۱۵	ΙÌο	con.	นวา	Clv	Ilo		
1		•		5	•	Asn			10					15			
Ser	Leu	Leu	Leu 20	Leu	Leu	Val	Val	Cys 25	Gly	Ile	Gly	Cys	Val 30	Trp	His		
Trp		His 35	Arg	Val	Ala	Thr	Arg 40	Phe	Thr	Leu	Pro	Arg 45	Phe	Leu	Gln	٠	
Arg			Ser	Arg	Arg	Lys 55		Cys	Thr	Lys	Thr 60		Leu	Gly	Pro		÷

Arg 65	Ile	Ile	Gly	Leu	Arg 70	His	Glu	Ile	Ser	Va1 75	Glu	Thr	Gln	Asp	His 80	
Lys	Ser	Ala	Val	Arg 85	Gly	Asn	Asn	Thr	His 90	Asp	Asn	Tyr	Glu	Asn 95		
Glu	Ala	Gly	Pro 100	Pro	Lys	Ala	Lys	Gly 105	Lys	Thr	Asp	Lys	Glu 110	Leu	Tyr	
Glu	Asn	Thr 115	Gly	Gln	Ser	Asn	Phe 120	Glu	Glu	His	Ile	Tyr 125	Gly	Asn	Glu	
	130		·	-	-	135			•		140		Ser	Glu	Val	
Pro 145	Gln	Asp	Glu	Asp	Ile 150	Tyr	Ile	Leu	Pro	Asp 155	Ser	Tyr				
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		100>									1 . 1					40
	_							_	-			_	cct Pro		_	48
													cac His 30			96
													gaa Glu	-	_	144
			-		-	_	_	_	-	-			cta Leu		-	192
	000	aca	cad	ata	ata	agc	ctt	aag	gac	aag	cta	gaa	ttt	gcc	ccg	240
65		-	_			_		Lys	Asp	Lys 75	Leu	Ğlu	Phe	_	Pro 80	

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Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn * 85 90

<210> 404

<211> 92

<212> PRT

<213> Homo sapiens

<400> 404

Met Trp Pro Val Phe Trp Thr Val Val Arg Thr Tyr Ala Pro Tyr Val 1 5 10 15

Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30

Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 45

Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 80

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn 85 90

<210> 405

<211> 255

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(255)

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Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro

1 5 10 15

cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc 96
Gln Pro Lys Arg Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro
20 25 30

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt. 144 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 35 40 45

535

gga atg aat toa gtt agc too att cag aac caa atg cag too aag gga 192 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 50 ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat 240 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 75 80 acg aag gcg gga tag 255 Thr Lys Ala Gly * <210> 406 <211> 84 <212> PRT <213> Homo sapiens <400> 406 Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 25 20 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 40 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 75 65 70 80 Thr Lys Ala Gly <210> 407 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 407 48

536

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_	att Ile	-					_	_	_		-			-	•	144
	ctt Leu 50	-	-						_	_			_	_		192
-	gag Glu		-	-	-		-	-	_	_	-	-	-		•	240
	agc Ser	-													•	249

<210> 408

<211> 82

<212> PRT

<213> Homo sapiens

<400> 408

Met Ala Ser Ser Gly Gly Ala Gly Ala Ala Ala Ala Ala Ala Ala Ala 1 5 10 15

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Arg Ile Leu Asn Thr Gly Leu Asp Met Glu Thr Leu Ser Ile Cys Val 35 40 45

Arg Leu Cys Glu Gln Gly Ile Asn Pro Glu Ala Leu Ser Ser Val Ile 50 55 60

Lys Glu Leu Arg Lys Ala Thr Glu Ala Leu Lys Ala Ala Glu Asn Met 65 70 75 80

Thr Ser

<210> 409

WO 01/29221

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PCT/US00/29052

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ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                       96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
             20
                                                      30
act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
                                                                      144
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
        35
                             40
                                                 45
ctg agg gtt tga
                                                                      156
Leu Arg Val *
     50
     <210> 410
     <211> 51
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Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
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Leu Arg Val
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     <211> 420
     <212> DNA
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PCT/US00/29052

538

WO 01/29221

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<221> misc_feature <222> (1)(420) <223> n = A,T,C or G														
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acc ctg gct cag gcg gag gag cag cag ccc tac ctg gag ggc tcc acc Thr Leu Ala Gln Ala Glu Glu Gln Gln Pro Tyr Leu Glu Gly Ser Thr 20 25 30	96													
gtt atg cgc ggg act cgc tgt ctg gca gag tac cac ctg ggg gat tat Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr 35 40 45	144													
gga cac gcc tgg aac agg tgt tgg gtg ctg gac agg gtg gac acc tgg Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp 50 55 60	192													
gct gtg gtc atg ttc att gat ttt gga cag ttg gcc acc atc cct gtg Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val 65 70 75 80	240													
cag tot otg ogo and tha gad ago gad gad tot totg acc atc oca occ Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro 85 90 95	288													
ctg act cag cca ttc atg ctg gag aaa gac att ttg agt tcg tat gag Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu 100 105 110	336													
gtt gtc cat cga atc ctc aaa ggg aaa atc act ggt gct ttg aac tcg Val Val His Arg Ile Leu Lys Gly Lys Ile Thr Gly Ala Leu Asn Ser 115 120 125	384													
gcg ttg cac atc cta aag ttt gaa gag tct aaa taa	420													

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Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys *
    130
                        135
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      <211> 139
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      <213> Homo sapiens
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     . <223> Xaa = Any Amino Acid
      <400> 412
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                                    10
Thr Leu Ala Gln Ala Glu Glu Gln Gln Pro Tyr Leu Glu Gly Ser Thr
                                25
            20
Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr
                            40
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
                                        75
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
                                105
Val Val His Arg Ile Leu Lys Gly Lys Ile Thr Gly Ala Leu Asn Ser
                            120
                                                125
Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys
    130
                        135
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			cca Pro 20										-	-	96
	-		att Ile			_				-					144
			ctt Leu			_	-								192
			tca Ser		-					_	_			•	240
		_	aag Lys	_		-		-		_				•	288
			aag Lys 100			_	-		-					•	336
			gcc Ala	_	-		-			-	-			•	384
_			ctg Leu ,				_								432
			caa Gln	Lys	-	_					_	_			480
			gaa Glu												528

	tgt Cys		-		_		_								-	576
_	agc Ser	-			-			_	-	_	_	-			-	624
	gaa Glu 210		-				-	-				-				672
	gag Glu			_							-	-			-	720
	gcc Ala															768
-	ggt Gly				-			tga *								795
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	</td <td>100></td> <td>414</td> <td></td>	100>	414													
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Leu	Leu	Met	Pro 20	Ala	Val	Ser	Val	Gly 25	Asn	Val	Gly	Gln	Leu 30	Ala	Met	
Asp	Leu	Ile 35		Ser	Thr	Leu	Asn 40		Ser	Lys	Ile	Gly 45		Phe	Tyr	
Thr	Asp 50		Leu	Val	Pro	Met 55	-	Gly	Asn	Asn	Pro 60		Ala	Thr	Thr	
	Gly	Asn	Ser	Thr			Ser	Пe	Asn			Val	Tyr	Ser		
65 Pro	Ser	Ara	lvc	Leu	70 Val	Δla	ا اھ ا	Gln	l eu	75 Ara	Ser	ء[]	Pho	110	80 L vs	
			•	85					90					95	-	
Tyr	Lys	Ser	Lys	Pro	Phe	Cys	Glu	Lys	Leu	Leu	Ser	Trp	Val	Lys	Ser	

			100					105					110			
Ser	Gly	Cys 115	Ala	Arg	Val	Пe	Val 120	Leu	Ser	Ser	Ser	His 125	Ser	Tyr	Gln	
Arg	Asn 130	Asp	Leu	Gln	Leu	Arg 135	Ser	Thr	Pro	Phe	Arg 140	Tyr	Leu	Leu	Thr	
Pro 145	Ser	Met	Gln	Lys	Ser 150	Val	Gln	Asn	Lys-	Ile 155	Lys	Ser	Leu	Asn	Trp 160	
Glu	Glu	Met	Glu	Lys 165	Ser	Arg	Cys	Ile	Pro 170	Glu	Ile	Asp	Asp	Ser 175	Glu	
Phe	Cys	Ile	Arg 180	Ile	Pro	Gly	Gly	Gly 185	Ile	Thr	Lys	Thr	Leu 190	Tyr	Asp	
Glu	Ser	Cys 195	Ser	Lys	Glu	Пe	G1n 200	Met	Ala	Val	Leu	Leu 205	Lys	Phe	Val	
Ser	Glu 210	Gly	Asp	Asn	Ile	Pro 215	Asp	Ala	Leu	Gly	Leu 220	Val	Glu	Tyr	Leu	
Asn 225	Glu	Trp	Leu	Gln	Ile 230	Leu	Lys	Pro	Leu	Ser 235	Asp	Asp	Pro	Thr	Val 240	
Ser	Ala	Ser	Arg	Trp 245	Lys	He	Pro	Ser	Ser 250	Trp	Arg	Leu	Leu	Phe 255	Gly	
Ser	Gly	Leu	Pro 260	Pro	Ala	Leu	Phe						-			
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	<2	220> 221> 222>		(2	225)											
_	<br 999 Gly		tta					_	-	-	-	-	_		_	48
	ctc Leu			-	-	_							-	-		96 ⁻
	atg Met	•	_				-	_	-			-	-			144

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aga ctc aag cag aga gac ctg gtg gcc act aga agc ttg gaa cag ccc 192 Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro 50 55 60 tca gtt gat agc aag gaa atg agg act cag tga 225 Ser Val Asp Ser Lys Glu Met Arg Thr Gln * 65 <210> 416 <211> 74 <212> PRT <213> Homo sapiens <400> 416 Met Gly Lys Leu Phe Trp Ile Ile Gln Met Asp Cys Val Gln Ser Gln 10 Glu Leu Leu Lys Ala Glu Thr Leu Ser Gln Leu Gly Ser Glu Arg Phe 25 Ile Met Arg Arg Ser Pro Leu Ala Val Ala Gly Phe Gln Asp Gly Gly Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro 55 60 Ser Val Asp Ser Lys Glu Met Arg Thr Gln 65 70 <210> 417 <211> 414 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(414) <400> 417 atg gag tac ata cag cag ttg aag gac ttt act acc gat gac ctg ttg 48 Met Glu Tyr Ile Gln Gln Leu Lys Asp Phe Thr Thr Asp Asp Leu Leu 1 5 10 15 cag cta tta atg tca tgt ccc caa gtt gaa tta att cag tgt ctc act 96 Gln Leu Leu Met Ser Cys Pro Gln Val Glu Leu Ile Gln Cys Leu Thr 20 25

aaa gag ttg aat gag aaa caa cca tct tta tct ttt ggt ctt gct ata Lys Glu Leu Asn Glu Lys Gln Pro Ser Leu Ser Phe Gly Leu Ala Ile 35 40 45	144													
ctt cat ctg ttc tct gca gac atg aaa aaa gtt ggc att aag cta ctt Leu His Leu Phe Ser Ala Asp Met Lys Lys Val Gly Ile Lys Leu Leu 50 55 60	192													
caa gaa atc aat aaa ggt ggg ata gat gca gta gaa agt ctt atg ata Gln Glu Ile Asn Lys Gly Gly Ile Asp Ala Val Glu Ser Leu Met Ile 65 70 75 80	240													
aat gat tcc ttt tgc tcc ata gaa aag tgg caa gaa gtg gca aat ata Asn Asp Ser Phe Cys Ser Ile Glu Lys Trp Gln Glu Val Ala Asn Ile 85 90 95	288													
tgt tca cag aat ggc ttt gac aaa tta tct aat gac atc acg tct att Cys Ser Gln Asn Gly Phe Asp Lys Leu Ser Asn Asp Ile Thr Ser Ile 100 105 110	336													
ctt cga tct cag gct gca gtt aca gaa att tct gaa gag gat gac gca Leu Arg Ser Gln Ala Ala Val Thr Glu Ile Ser Glu Glu Asp Asp Ala 115 120 125	384													
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Gln Leu Leu Met Ser Cys Pro Gln Val Glu Leu Ile Gln Cys Leu Thr 20 25 30														
Lys Glu Leu Asn Glu Lys Gln Pro Ser Leu Ser Phe Gly Leu Ala Ile 35 40 45														
Leu His Leu Phe Ser Ala Asp Met Lys Lys Val Gly Ile Lys Leu Leu 50 55 60														
Gln Glu Ile Asn Lys Gly Gly Ile Asp Ala Val Glu Ser Leu Met Ile														

65					70					75					80	
Asn	Asp	Ser	Phe	Cys 85	Ser	He	Glu	Lys	Trp 90	Gln	Glu	Val	Ala	Asn 95	Ile	
Cys	Ser	Gln	Asn 100	Gly	Phe	Asp	Lys	Leu 105	Ser	Asn	Asp	Пe	Thr 110	Ser	Ile	
Leu	Arg	Ser 115	Gln	Ala	Ala	Val	Thr 120	Glu	Ile	Ser	Glu	Glu 125	Asp	Asp	Ala	
Val	Asn 130	Leu	Met	Glu	His	Val 135	Phe	Trp								
				o sap	oiens	5										
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			cat His 20									-	-			96
			ggc Gly							-			-	_	-	144
			atg Met													192
			cag Gìn													240
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546

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547

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Val Pro Glu Asp Thr Val Pro Lys Ser Asp Pro Arg Gly Gly Arg Lys
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